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Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*December* 9, 1955]

Coarctation of Aorta (Surgical Repair) with Aortic Valve Disease.—D. WEITZMAN, M.D.

Miss L. D. B., schoolmistress aged 23, complaining of undue fatigue after effort. She was referred by Dr. H. Aston.

A cardiac abnormality was first noted at the age of 5. When aged 12 she developed acute rheumatic fever and was admitted to the Queen Elizabeth Hospital, Hackney, where signs of aortic valvular disease were noted. Following recovery, her activity was restricted on medical advice and she remained free of dyspnœa or other symptoms until early 1955.

Examination then revealed B.P. 180/70, with collapsing radial and absent femoral pulses, and palpable collateral vessels around the scapulæ. There was marked left ventricular hypertrophy with systolic and early diastolic murmurs and thrills over the entire prækordium, giving the impression of a continuous bruit in the third and fourth left interspaces. The systolic murmur was maximal at the aortic area, where it was rough and harsh, and whence it radiated into the neck. X-ray showed considerable enlargement of the left ventricle (Fig. 1) and rib notching. No calcification was detected in the aortic valve on screening. The electrocardiogram showed left ventricular preponderance in an electrically vertical heart. Because of the "continuous" bruit, cardiac catheterization was carried out, in order to exclude patency of the ductus arteriosus. The catheter revealed no evidence of any left-to-right shunt and the right-sided pressures were normal. Angiocardiography confirmed the presence of a coarctation just distal to the origin of the left subclavian artery and demonstrated dilatation of the ascending aorta with a localized aneurysmal bulge on its anterior surface (*see* Figs. 1 and 2).

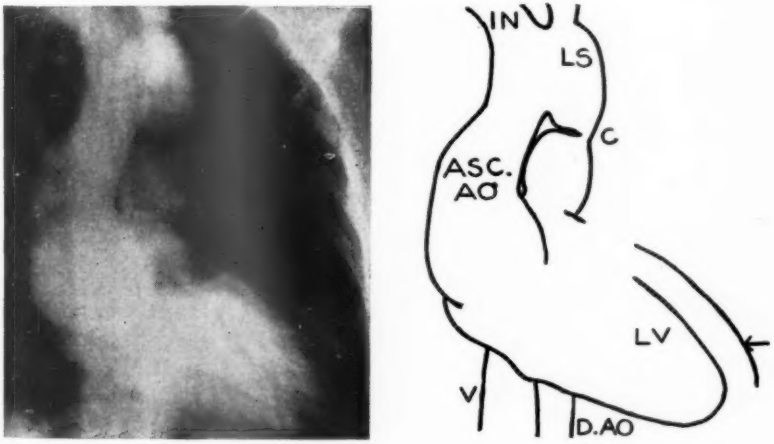
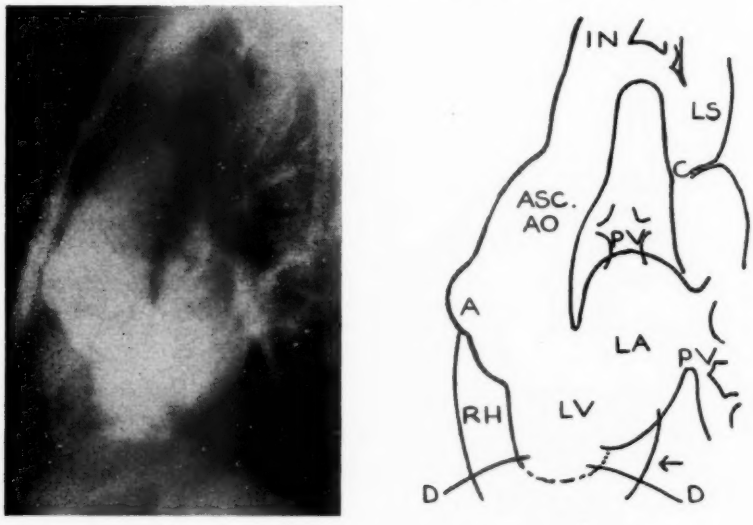


FIG. 1A and B.—Antero-posterior view of angiocardiogram 9 seconds after injection of contrast medium. IN = innominate artery, LS = origin of dilated left subclavian artery, C = site of coarctation, ASC.AO = ascending aorta, LV = left ventricle, D.AO = descending aorta, V = edge of vertebral column. The arrow points to the outer surface of the left ventricle and indicates the thickness of the muscle.

The unusual feature in this case is the very free aortic regurgitation, for which both congenital malformation and rheumatic damage may be responsible. (No information is available as to whether any aortic valve lesion was present prior to the attack of rheumatic fever.) A bicuspid aortic valve, which readily becomes incompetent (Peacock, 1866), is often found in cases of coarctation, the reported incidence being as high as 42% (Reifenstein *et al.*, 1947). These authors also confirmed the observation of Hamilton and Abbott (1928) concerning the frequent association of medial degeneration of the aorta with

coarctation and a bicuspid valve, with the consequent risk of aortic rupture. The generalized but asymmetrical dilatation of the ascending aorta, as well as the localized bulge, strongly suggest the presence of medial degeneration in this patient.

The harsh aortic systolic murmur and thrill, conducted to the carotids, are suggestive of aortic stenosis, but the pulse pressure indicates that any such lesion is not significant. The stenosis might be sub-aortic. Taussig (1947) states that "the association of coarctation with sub-aortic stenosis and aortic incompetence is so frequent as to constitute a definite clinical entity" but describes only one case and quotes one other reported by Hamilton and Abbott (1928). Donzelot and d'Allaines (1954) refer to this combination as the "syndrome de Taussig". 2 of the 5 cases of aortic stenosis with coarctation reported by Smith and Matthews (1955) had free aortic incompetence, judged by the pulse pressures.



A B

FIG. 2A and B.—Left lateral view of angiocardiogram 8½ seconds after injection. PV = pulmonary veins, LA = left atrium, RH = right heart chambers, D = diaphragm. The arrow again indicates the epicardial surface of the left ventricle. A = aneurysmal protrusion on anterior aspect of ascending aorta.

The free aortic leak and the localized aneurysmal bulge were regarded as additional indications for surgical attack on the coarctation since it was felt that relief of the obstruction would reduce the reflux and, by lowering the intra-aortic pressure, diminish the risk of rupture of the aneurysm. The operative mortality in these cases is high, and Gross (1953) regarded aortic regurgitation of serious extent as a contra-indication to surgery in coarctation. However, Tubbs (1955) considers that the use of controlled hypotension during operation greatly reduces the risk.

Operation was carried out on 10.10.55 by Mr. O. S. Tubbs. The constriction was half an inch in diameter. There was free regurgitation at the aortic valve. The ductus arteriosus was impervious. The stricture was excised and an end-to-end anastomosis was performed. Post-operative progress was satisfactory.

She was seen two months after operation, when the aortic leak appeared to be less marked. The radial pulse was still collapsing in character, but B.P. was now 125/60. The femoral pulses were palpable, with slight delay. Disability remained minimal.

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Long-standing Superior Vena Cava Obstruction with Notching of Ribs from Dilated Intercostal Veins.—E. MONTUSCHI, M.D., M.R.C.P.

E. C., female, aged 61. British.

Admitted 13.10.55 with an attack of severe breathlessness and vague pain in the chest.

History.—1916, superior vena cava thrombosis of undetermined ætiology. Effort tolerance very limited since then and has had recurrent attacks of breathlessness. Has also been troubled by varicose veins.

On examination.—Fairly marked cyanosis. Some puffiness of the face, fixed distension of the jugular veins. Very marked collateral circulation of the chest and abdomen. Pulse 90, blood pressure 140/90. Heart not enlarged, sounds normal. Normal pulsation of femoral arteries. Hb 93% with normal film. ECG shows small secondary R in V1 and V2. Arm to tongue circulation time 45 seconds. X-ray of chest: Left ventricle prominent and aorta unfolded. Clear lung fields. There is notching of the undersurface of the left 6th and 7th ribs (Fig. 1). The radiologist in reporting this finding queried the presence of coarctation of the aorta. As aortic coarctation can be confidently excluded it seems most likely that the sign is due to erosion of the ribs by dilated intercostal veins. Dr. Peter Kerley (1955) kindly confirmed this opinion.

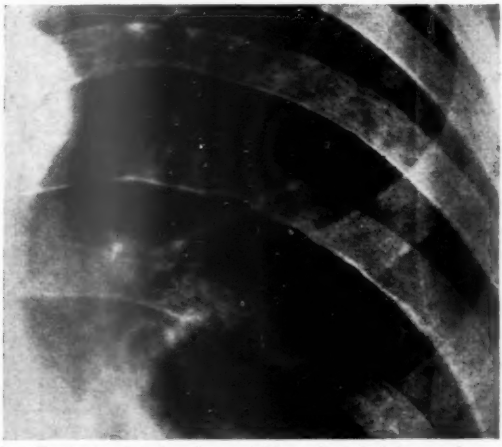

FIG. 1.—Contact print showing notching of underlying surface of ribs.

Comment.—Erosion of the ribs by dilated intercostal veins in chronic superior vena cava obstruction has been described by Kerley (1950) but must be of very rare occurrence. This patient is also interesting because of the length of survival with complete superior vena cava obstruction.

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Cushing's Syndrome with Polyneuritis.—RAYMOND GREENE, D.M., and D. CROOKE MORGAN, M.B., B.Sc.

Female, aged 31. Shop assistant. Referred to New End Hospital by Dr. Emyr Jones of the Caernarvon and Anglesey General Hospital on 12.8.55.

There had been a gradual onset of depression and fatigue over two or three years, and for about two years her friends had remarked on the bluish tinge of her face. During the past nine months she had shown an increasing tendency to spontaneous bruising. She had had amenorrhœa, hypertrichosis of the face, and a constant severe pain between the shoulder blades. This had spread to the lumbar region after an attack of "bronchitis" six months before, when her feet and legs began to swell. She became gradually incapacitated by the pain, until in April she became bedridden and was admitted to the Caernarvon and Anglesey Hospital where a diagnosis of Cushing's syndrome was made. She was discharged, but in August was readmitted in a coma due to barbituric poisoning. From this she made a good recovery and was then transferred to New End Hospital.

On examination she presented the characteristic appearance of severe Cushing's syndrome (Fig. 1). The degree of ecchymosis was extreme and hæmatomata were present on both legs. One of these, under the skin of the right calf, was exuding outwards and also tracking up the lateral aspect of the thigh (Fig. 2). Her blood pressure was 180/130. Foot

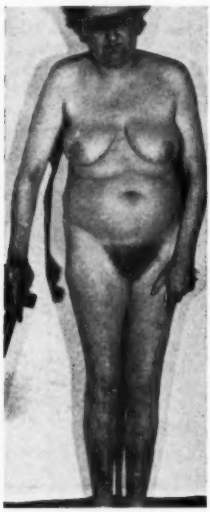

FIG. 1.

FIG. 2.

drop was present on the right. Examination by Dr. Redvers Ironside showed wasting of the right and left interossei, thenar and hypothenar muscles. There was weakness of the right hand-grip but no wrist drop. She was unable to lift either leg with the knees straight, and flexion of the right knee was feeble. There was slight weakness of dorsiflexion of the left knee. There was loss of sensation to cotton-wool on the skin of the right foot. Knee-jerk was absent on the left and faint on the right. Both ankle-jerks were absent. The nervous system otherwise was normal.

Further examinations.—Positive Hess test. Hæmatological and biochemical examinations disclosed nothing abnormal except for a polymorphic leucocytosis of 15,900, and a mildly diabetic glucose tolerance curve. The 17-ketosteroids excretion was normal (16·3 mg./24 hr.). X-rays showed a normal pituitary fossa. Severe osteoporosis was present throughout the skeleton, and there were many collapsed vertebral bodies in both dorsal and lumbar areas. The protein content of the ventricular fluid was 10 mg., and of the spinal fluid 30 mg. per 100 c.c.; C.S.F. was otherwise normal.

After preparation with cortisone and methyl testosterone, a total adrenalectomy was performed by Mr. J. E. Piercy. The weight of the adrenals totalled 30 grams.

Histology.—There was diminution of the lipoid content and abundant fuchsinophil granules were present in the zona fasciculata and zona reticulosa.

Convalescence was interrupted by a sudden severe intestinal hæmorrhage, after which the hæmoglobin fell to 39%. She recovered after transfusion, and the incident was not repeated. A barium meal performed later showed no abnormality.

9.12.55: General health excellent; B.P. 120/90 and skin rapidly returning to normal. No improvement in the polyneuritis; there had not yet been time for any improvement in the osteoporosis. Glucose tolerance curve almost normal.

The association between Cushing's syndrome and polyneuritis has only recently been observed. Two cases of Cushing's syndrome with the Guillain-Barré syndrome are the only ones in the literature (Dynes, 1955), but Dr. Redvers Ironside has mentioned a further case with polyneuritis under the care of Sir Daniel Davies.

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Mr. Selwyn Taylor asked why total ablation of the adrenals was performed on this patient and why it was necessary to do this in two stages. He found that with the "jack-knife" position it was technically easy to operate on both adrenals on the one occasion and it was also possible to leave behind about 1/6 to 1/8 of one of the glands. By this means the patient only had to have one operation and it was often possible to do without long-term cortisone replacement therapy afterwards.

Dr. Raymond Greene said that the frequency of recurrence after a subtotal adrenalectomy was uncertain. Dr. R. G. Sprague, of the Mayo Clinic (1953, *Proc. R. Soc. Med.*, **46**, 1070), considered that recurrence was likely, whereas Dr. L. Soffer, of New York, reported successful results after a unilateral adrenalectomy, provided it was followed up by X-ray treatment to the pituitary.

Benign Spinal Tumour in Elderly Patients (Two Cases).—D. L. B. FARLEY, F.R.C.S. (for LESLIE C. OLIVER, F.R.C.S.).

Case I (referred by Dr. E. C. O. Jewesbury).

Female, aged 75. Quite unable to walk or stand on examination 7.10.55. There had been weakness of both legs since August 1944, associated with some involuntary twitching which kept her awake at night.

On examination.—Spastic paraplegia. No definite sensory change. Plain X-ray of spine: No bone erosion seen. Lumbar puncture: Pressure 60 mm. of water. Queckenstedt's test showed a complete block. C.S.F. contained 60 mg. protein and less than 1 cell per 100 c.c. Myelogram showed complete block at the level of D.2.

Operation (10.11.55).—An extradural tumour was found lying on the posterior and left lateral aspects of the spinal cord at the level of the dorsal second vertebra. It was scraped off the dura with some difficulty and an apparently complete removal achieved. The cord was seen to pulsate after this.

A frozen section in the theatre showed psammomatous meningioma. This was confirmed on routine histology.

Convalescence.—Patient able to walk a month after operation. Some difficulty in micturition, this being a new symptom. Further progress has been rapid.

FIG. 1 (*Case II*).—Myelogram X-ray showing the block between T.8 and T.9 vertebræ together with erosion of the posterior surface of the body of T.7 by the tumour.

Case II (referred by Dr. E. C. O. Jewesbury).

Female, aged 73. Unable to walk in September 1952 after a three-month history of weakness of the legs. There was some difficulty in micturition.

On examination.—Upper motor-neurone weakness of both legs, especially the right. There was some impairment of sensation below the 8th thoracic segment. Right plantar response extensor, left flexor. Lumbar puncture: Pressure 135 mm. Sluggish Queckenstedt response. Protein 250 mg. 3 white cells per 100 c.c. Myelogram showed complete block at D.8 (Fig. 1).

The legs became almost completely paralysed, and there was some pain in the right lower leg.

Operation (12.12.52).—Extramedullary tumour found compressing the cord from the right side at the level of T.7–9. Removal complete.

Convalescence.—Movement returned to the right leg on the fifth post-operative day. Vibration sense recovered. She was able to walk unaided two months after operation, and there was full return of bowel and bladder function. There are now no abnormal signs.

The pathology was the same as that in the previous case.

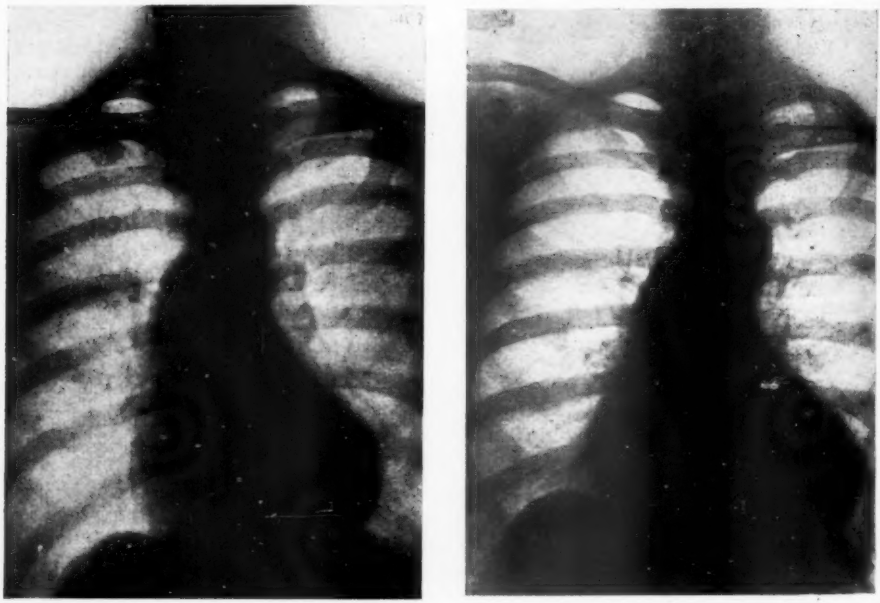
[*February* 2, 1956]

Two Cases of Fallot's Tetralogy, Shown at the Section in 1929, Exhibiting Unusual Longevity.—D. EVAN BEDFORD, M.D., F.R.C.P.

In 1929, three adult cases of Fallot's tetralogy, aged 32, 34 and 26 respectively, were shown by me at the Clinical Section. Case I survived to the age of 52 and the after-history and post-mortem findings are given. Case II has not been traced. Case III is still alive and is presented to-day at the age of 52.

Case I.—Mrs. B. M., shown at R.S.M., aged 32, in December 1929. She continued to attend my Out-patient Clinic, Middlesex Hospital, regularly and was admitted to Hospital on four occasions, namely in 1933, twice in 1947, and finally in 1948. She died on 5.3.48 aged 52 years and 8 months. She suffered from increasing cyanosis, attacks of dyspnœa, and cerebral symptoms which became more severe during her last year, namely giddiness, vomiting, headaches, transient loss of vision, and drowsiness. The heart became larger and during the last four years (*see* Fig. 1A, B) she had a slight degree of congestive failure with

1929, aged 32 1947, aged 51

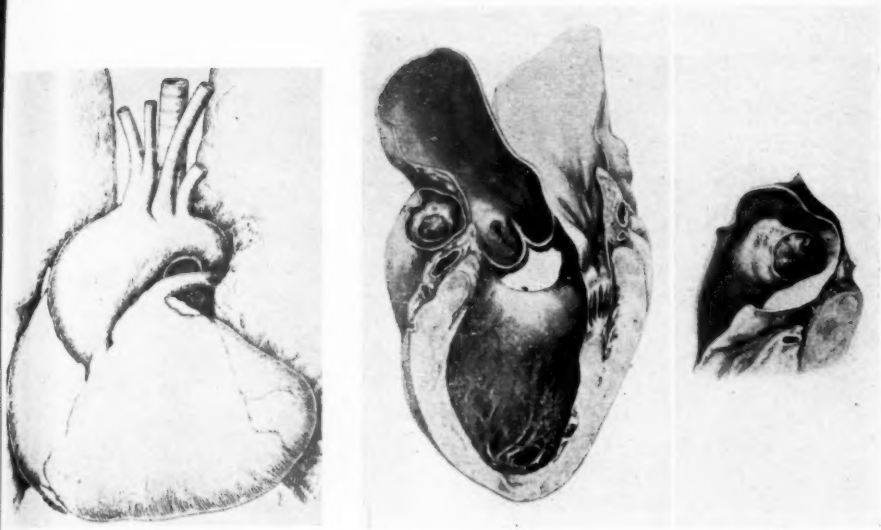


A B

FIG. 1 (*Case I*).—Radiographs when at the age of 32(A), and 51 (B), showing a prominent ascending aorta, a pulmonary bay, and a heart of *cœur en sabot* configuration. The heart has enlarged to the right slightly in the course of nineteen years.

raised venous pressure, enlarged liver, and œdema. The spleen was palpable. Blood counts showed red cells up to 9,000,000; Hb. 126%. She was treated with digitalis, Mersalyl injections, and periodic venesection. Eventually she became increasingly drowsy and died in coma in her 53rd year.

Post-mortem.—The ascending aorta was much enlarged. There was pulmonary valvular stenosis, the valves forming a conical diaphragm, convex upwards, and it was difficult to find any passage as the diaphragm was surmounted by organized ante-mortem thrombus. There was a ventricular septal defect, semilunar in shape, $3{\cdot}5 \times 1{\cdot}5$ cm. situated just below the aortic cusps in the membranous septum. The aortic cusps were large and slightly adherent at the commissures. The aorta communicated with both ventricles, the ascending part was enlarged, 5 cm. in diameter, and the aorta narrowed abruptly at the isthmus where it was 1·8 cm. in diameter. The right auricle was dilated, and the right ventricle hypertrophied (Fig. 2A, B). The main pulmonary branches were of normal size and thin-walled. No enlargement of the bronchial arteries was found, but the first right aortic intercostal was enlarged. The heart weighed 17 oz.



A B C

FIG. 2 (*Case I*).—A, Specimen drawn *in situ*, showing large ascending aorta and abrupt narrowing at the isthmus; hypoplastic pulmonary artery. B, Opened heart with wall of left ventricle removed to show septal defect below root of overriding aorta, and pulmonary valvular stenosis. C, The stenosed valve forms a conical diaphragm capped by organized thrombus.

Case III.—Mrs. M. F., shown at R.S.M. aged 26, in 1929, and again to-day, now aged 52. Since 1929 she has attended hospital regularly and has been admitted on seven occasions, the last time in 1953. In 1938 she got married and sterilization was performed. Later she developed recurrent bacilluria and renal investigation suggested a horse-shoe kidney. She has suffered a good deal from dyspepsia, but her main complaint has been severe headaches and giddiness treated by periodic venesection with benefit. Blood counts have shown the red cells up to 8,900,000, and the Hb up to 170%, the last 143%.

Signs.—Cyanosis and clubbing of the fingers. B.P. 120/80 mm. There is a basal systolic murmur and thrill, maximum at the 2nd right interspace. The second sound is single.

X-ray shows a right-sided aortic arch, a sabot-shaped heart, and a pulmonary bay; the heart has enlarged since 1929 (Fig. 3A, B). An angiocardiogram shows premature filling of the aorta from the right ventricle, a right-sided aortic arch, and a high infundibular stenosis with a small infundibular chamber. The electrocardiogram shows right ventricular hypertrophy. Arterial oxygen saturation 88%.

She is able to do some housework and is not unduly breathless. Her cyanosis varies from time to time but on the whole it is no worse than in 1929.

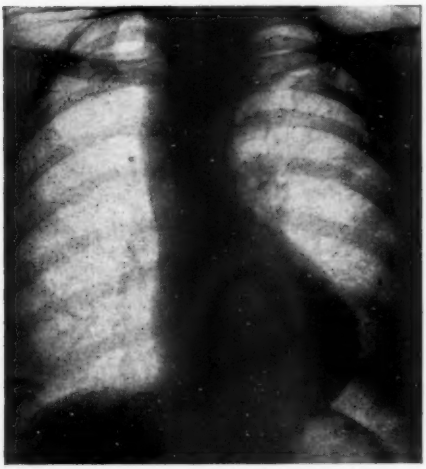
Comment.—The post-mortem findings in the first case exemplify the aortic enlargement which is always found in Fallot's tetralogy; in this case the ascending aorta appeared almost aneurysmal, and the usual abrupt diminution in calibre at the isthmus is well shown. It also exemplifies a pure valvular stenosis occurring in Fallot's tetralogy such as would have been suitable for valvotomy.

Two of the three cases shown in 1929 had a right-sided aortic arch, and I mentioned then that I had seen four cases of this combination which, to-day, is recognized as common, occurring in 20–25% of all cases of the tetralogy.

Only 5–10% of all cases of Fallot's tetralogy reach adult life (apart from surgical treatment) and survival to over 50 is exceptionally rare. The best-known example of longevity in this disease is that of Henry Gilbert, the American composer and musician, who died aged 59 years and 8 months, with hemiplegia (White and Sprague, 1929). Brown (1950) cites Brumlik's case which survived to the age of 62 as the oldest. Lian and Fleury (1949) reported the case of a female dressmaker who worked regularly up to the age of 40, and who died at the age of 55 in coma; the diagnosis was confirmed at necropsy.

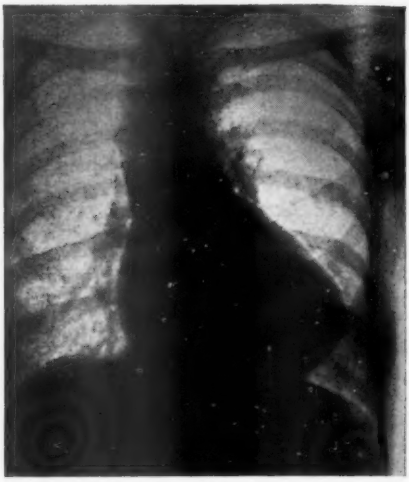
Those who do reach adult life appear to suffer increasingly from cerebral symptoms such as giddiness, headache, transient palsies, drowsiness, and finally coma. These symptoms arise from cerebral anoxia and, in my cases, were relieved temporarily by venesection.

1929, aged 26



A

1949, aged 45



B

FIG. 3 (*Case III*, aged 52).—A, Radiograph aged 26, and B aged 45, showing pulmonary bay, *cœur en sabot* shape, and right-sided aortic arch with prominent ascending aorta. The heart has enlarged slightly in eighteen years.

It is general experience that the results of surgical treatment of Fallot's tetralogy in adults are poor. We do not know yet what the expectation of life may be in younger patients after surgical treatment.

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Werner's Syndrome.—D. C. DEUCHAR, M.D., M.R.C.P.

In 1904 Werner described, under the title "Cataract in connexion with Scleroderma", four siblings suffering from the syndrome which now bears his name. This patient has nearly all the features of this rare and interesting condition.

Mrs. A. R., aged 56. The patient had unusually thin legs when a child but led a normal active life until about fifteen years ago. Menstruation started at 15 years and she has had two children; the menopause occurred at the age 42. Some greying of the hair was noted at 16 years of age and was complete at 40. The patient is not clear when the feet first became painful, but they were so when shininess of the skin and deformity of the toes of the right foot developed at the age of 40; all these toes were amputated three years later in 1943. The left foot became similarly affected about two years later. Visual difficulties were first noted in 1942 and operations for bilateral cataracts have since been performed.

Her present disability is due partly to deformed feet and ankles, and partly to a recent fracture of the left femur.

One of the patient's sisters (there are 5 siblings), now 41, has a similar habitus, went grey recently and now is developing bilateral cataracts.

On examination.—Bilateral cataract extractions have been performed. The hair of the head is fine and white; axillary hair is absent and pubic scanty. The trunk is well covered with subcutaneous fat and the abdomen is rather protuberant; by contrast the limbs, especially the legs, are grossly wasted, both fat and all muscle groups being involved. The skin over most of the limbs is soft and loose but on the feet it is tight and dry; ulceration is present on both feet and ankles. The toes of the right foot have been amputated. The left toes are "clawed" and fixed; movement at the ankles is very limited (Fig. 1). The fingers of both hands are stiff and fully extended only with difficulty. The remaining joints are normal. There are no other abnormalities and, in particular, in the nervous system the cranial nerves are normal; power, despite wasting is quite good, tendon reflexes are present (except at the ankles) and there is no sensory loss.

Investigations.—Urine, normal apart from a slight excess of calcium to Sulkowitch's reagent. Blood picture normal. Serum calcium (15.5.53) 10·1 and (17.11.55) 11·8 mg.%. Serum cholesterol 360 mg.%. Glucose tolerance test: Fasting blood sugar 97, two hours 200, two-and-a-half hours 156 mg.%, indicating impaired glucose tolerance. B.M.R. (10.8.50) −3% and (5.9.51) −8%. X-rays: The bones of the feet show severe osteoporosis and there are several deposits of soft tissue calcification.

Comment.—Werner encountered his patients whilst working in the ophthalmological clinic as they presented with cataracts; he described the associated clinical features occurring in these four siblings, laying stress on the bodily habitus (short stature, well-covered trunk and wasted limbs) and skin changes over the feet. Subsequently this syndrome became confused in the Continental literature with a number of somewhat related disorders, notably Rothmund's syndrome. In a detailed review Thannhauser (1945) analysed the reported cases, described five more and clearly distinguished Werner's syndrome from the other conditions. He listed the features of the syndrome as the bodily habitus, premature greying of the hair, early baldness, the skin changes over the feet with tendency to ulceration, presenile cataract, hypogonadism, a tendency to diabetes mellitus, subcutaneous and arterial calcification, osteoporosis, its occurrence in siblings and development of the clinical picture in middle adult life. From his study he concluded that the skin changes were not true scleroderma.

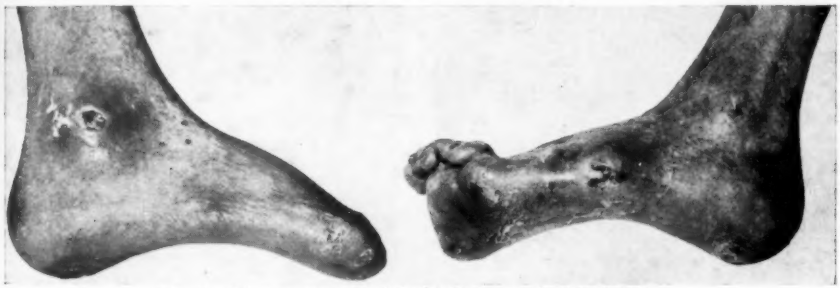

FIG. 1.—The appearance of the right foot and of the left foot.

There appear to be only two reports of this condition in the British literature: Williams (1949) presented a case to the Dermatological Section of this Society and more recently Ellison and Pugh (1955) described two examples in sisters.

The nature of this disease remains obscure but it seems unlikely to be primarily an endocrine or renal disorder; it is probably an inherited dystrophic condition similar to dystrophia myotonica, with which it has several features in common.

I am indebted to Dr. A. C. Hampson, under whose care this patient is, for permission to present her before the Society.

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Giant Cyst of Liver.—M. C. WATERFALL, F.R.C.S.

Mrs. A. G., aged 76, was admitted to Kingston Hospital on January 5, 1956, complaining of breathlessness and abdominal pain.

History of present complaint.—Two weeks before admission, whilst returning from a church tea party, she noted sudden breathlessness causing her to stop walking. She was helped home and went to bed where she has remained ever since. For the past two weeks she has also noticed vague generalized abdominal pain, aching in character, and present mainly on the right side of the abdomen. It is not affected by eating. Bowels have always been constipated—no recent change. Relatives say she has got thinner recently.

Previous medical history.—No illnesses. Has never been abroad. Four children.

On examination.—She was thin and pale. There were no abnormal palpable glands. No clubbing. Jugular venous pressure was normal. C.V.S.: Systolic murmur at the apex. Pulse regular 80. B.P. 250/120. Chest: Good dry air entry on the left. On the right few fine crepitations in the axilla. No air entry over the right lower lobe posteriorly. Percussion note normal. Considerable prominence of the right lower ribs in the axilla and anteriorly.

Abdomen : Distended. Small reducible umbilical hernia. There was a very large mass filling the right hypochondrium extending down to the umbilicus as far as the anterior superior iliac spine. It moved a little with respiration. The edges were firm and felt irregular. Lying on top of this mass, just below the right costal margin, there was a soft area which felt cystic and about 3 in. in diameter; this moved with the main mass. Rectal examination normal.

Investigations.—Chest X-ray: The right lower ribs were splayed out. The right diaphragm was very high (it was, unfortunately, not screened) (Fig. 1). There was some calcification

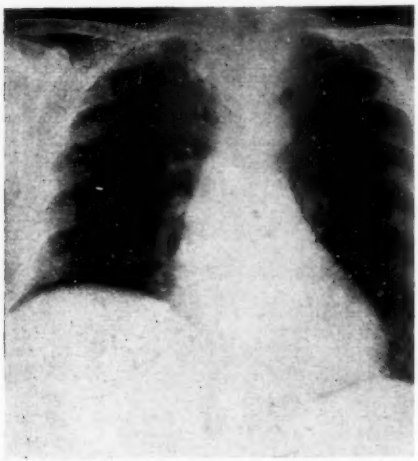

FIG. 1.—Pre-operative X-ray to show splaying of ribs and raised diaphragm.

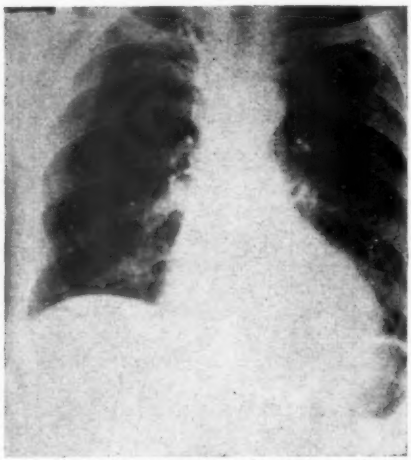

FIG. 2.—Post-operative chest X-ray—the diaphragm has descended.

of the right apex and hilum. Straight X-ray of the abdomen showed the hepatic flexure of the colon to be displaced downwards. There was a soft tissue mass present in the right upper quadrant of the abdomen. Intravenous pyelogram—left kidney functioning normally. No secretion demonstrated on the right. Blood urea 28 mg.%. Hæmoglobin 80%.

Operation (9.1.56).—Excision of cyst of liver. Transverse incision dividing the right rectus muscle. There was an enormous cyst of the liver pushing the diaphragm up and extending down to within an inch of the bifurcation of the aorta. The liver substance was pushed over to the left of the abdomen causing great distortion of the falciform ligament and the gall-bladder lay well over to the left of the mid-line. The cyst was punctured and ten pints of dark brown fluid sucked out together with about a pint of old blood clot. The cyst was gently enucleated from the liver and several small branches of the hepatic artery divided. There was a thin rim of liver substance over the top of the cyst between it and the diaphragm. A small hole was torn in one hepatic vein just as it entered the inferior vena cava; this was repaired. After removal of the cyst the right kidney was seen. There was another cyst about 2½ in. in diameter on its upper pole; this was left *in situ.* The wound was closed with two drains.

Progress.—The day after operation there was good air entry over the right lower lobe. The liver edge was just palpable at the costal margin Fig. 2). Blood pressure was 190/110. Convalescence was uneventful and she was discharged well. An intravenous pyelogram taken after operation shows secretion in both kidneys.

Comment.—About 250 cases of solitary non-parasitic cysts of the liver have been reported; at least half of them were associated with cysts of the kidney. Most have been considerably smaller than this one, but in 1892 Bagot reported a cyst containing 2½ gallons which was found in a fœtus and complicated its delivery. The commonest symptom is pain in the right upper quadrant of the abdomen and I cannot find another case in which the main complaint was of dyspnœa. Solitary cysts of the liver are usually retention cysts, due to obstruction of a small bile duct and it was thought that this was the ætiology in this case. Absence of secretion in the right kidney was first considered to be due to pressure of the cyst on the renal vessels, but it is possible that the fluid in the cyst obscured secretion in the right kidney. Section of the cyst shows its wall to be composed of fibrous tissue containing a number of small bile ducts.

United Services Section

President—Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

[*December* 1, 1955]

DISCUSSION ON IMMUNIZATION AGAINST TUBERCULOSIS IN THE ARMY

Colonel L. R. S. MacFarlane:

During the past thirty years it has been shown that the only form of protection against tuberculosis is afforded by a healed primary complex caused originally by living *Mycobacteria tuberculosis*.

Since, however, these organisms can and do disseminate from the primary complex before it heals and give rise to more serious forms of tuberculosis, the giving of a live vaccine is fraught with danger.

Calmette and Guérin evolved a culture so attenuated that it was thought to be safe to give as a vaccine as it was supposed to be weak enough not to disseminate from a primary complex and yet potent enough antigenically to produce protection.

Acting on the principle that most persons in early life acquire sufficient subliminal infection to produce immunity against a primary major infection later on, the vaccine was supposed to supply this subliminal infection in persons who had not acquired it otherwise—"tuberculin-negative" persons who failed to give an allergic response to Old Tuberculin in low dilution.

In 1927 Heimbeck and Wallgren showed in effect that such a culture could and did produce just such a primary focus or lesion in the skin of the leg or arm of a tuberculin-negative person, and rendered them Mantoux or tuberculin positive.

Calmette and Guérin actually gave this vaccine by mouth and this still obtains in some countries but we prefer the intradermal method of Wallgren which supplanted the subcutaneous route of Heimbeck, the latter being prone to give rise to local abscesses.

France and the Scandinavian countries are the pioneers in this field and they claim no cases of miliary tuberculosis have developed in infants thus treated [1].

Not long after the war, the Ministry of Health provided facilities for BCG to be given by accredited physicians to certain groups of patients: (1) Children born into families where there are open cases of tuberculosis. (2) Nurses. (3) Medical students.

The value of BCG in this country will take time to assess and Medical Research Council trials on school children are still in progress. Nevertheless Heaf showed that amongst inhabitants of Bornholm Island, BCG vaccination of Mantoux negatives has greatly reduced the incidence and mortality of tuberculosis [2]. In Dublin the Child Contact Protective Service, which includes BCG amongst its activities, has caused an 82% decrease in childhood deaths from tuberculosis in that city [3]. Gaisford, in a series of infant immunizations in Manchester, also gives encouraging morbidity reduction figures [6].

In 1950 it was decided to introduce BCG into the Army—for a start the following to be offered vaccination if Mantoux negative: (1) All regular R.A.M.C. officers and other ranks. (2) All officers and other ranks of Queen Alexandra's Royal Army Nursing Corps.

National Service officers and other ranks of the R.A.M.C. would also be given the opportunity especially if working in tuberculosis wards, laboratories or post-mortem rooms and, in fact, such Mantoux-negative personnel would *have* to be precluded from working in these localities until protected.

When the scheme started it was found possible to provide vaccination for Mantoux-negative Service children living at risk with open tuberculosis parents, when they were inconveniently situated as regards civil BCG schemes.

In 1954 the scheme was extended to include the Royal Army Dental Corps, physiotherapists and members of the St. John Ambulance and British Red Cross Society.

Soon after the introduction of this scheme, dried BCG vaccination was undertaken for members of the Fiji Forces, Gurkhas and Seychellois. Captain Robinson discusses this.

The initial arrangements were entrusted to Lt.-Col. A. J. N. Warrack but the implementation of the scheme fell to myself and could be said to have started with effect from January 1, 1951.

The arrangements were as follows:

(1) *Q.A.R.A.N.C.*—In the first week of their training these girls were Mantoux tested with 0·1 ml. of 1/10,000 Old Tuberculin intradermally (0·01 mg. O.T.) the test being read after seventy-two hours. Negatives were given another Mantoux test with 1/100 Old Tuberculin. Anyone still negative was offered BCG. Those requiring and requesting BCG had first to have a clear chest X-ray. BCG was

given intradermally into the upper deltoid area of skin—the dose being 0·1 c.c. (BCG vaccine contains 0·5 mg. organisms by weight per c.c.). Six weeks later a follow-up Mantoux was given using a 1/100 dilution Old Tuberculin, and thereafter a yearly follow-up, using 1/1,000 dilution or 1/100 dilution.

(2) *R.A.M.C.*—An exactly similar procedure was carried out at the R.A.M.C. Depot.

BCG vaccine was flown to the Ministry of Health fortnightly from Copenhagen and thence supplied to the Leishman Laboratory, Aldershot. Sessions were therefore held on fixed days at fortnightly intervals—in the mornings at the Q.A.R.A.N.C. Depot, Hindhead, and in the afternoons at the R.A.M.C. Depot, Crookham.

As already mentioned the scheme was under the control of the Assistant Director of Pathology, Southern Command, assisted by the pathologist at the Connaught Military Hospital, Hindhead, and this arrangement still largely continues.

At first, all other personnel requiring BCG had to attend one of these two centres, even from other Commands in the United Kingdom, and BCG was only in very special circumstances redirected, chiefly where children needed it. It was felt that in the early days BCG should be in the hands only of those running the scheme and the greatest of care in sterilizing equipment, keeping dirty and clean equipment well apart, &c., was exercised.

Once the person was converted, duplicate BCG cards were completed—one copy being held by the A.D.P. Southern Command, the other by the person's unit. This latter is now, however, held by the Officer-in-Charge Records. Care of these cards is of immense value in following up the patients. It was incumbent on the unit to which the person was posted to arrange an annual follow-up with the local pathologist and to have the result reported to the A.D.P. Southern Command for entry on his card. It has, of course, been hard to follow those who have left the Army but civil authorities have been very helpful in this respect.

Infants when vaccinated can safely take 0·15 c.c. or 0·2 c.c. which is best given in two insertions either both into one deltoid skin area or one on each side. Children have the adult doses. Some difference of opinion, however, exists concerning the necessity for a *double* dose in infants and, in the Army, we in fact give 0·1 ml. in two injections on the same side.

All Mantoux-negative personnel awaiting BCG should be free from all known or likely contact with tuberculosis for about six weeks before BCG and after BCG until they convert, and this was found fairly easy whilst the persons were still at their Depots. It became more of a problem to supervise them when they went to hospital units, or, as occasionally happened, left the Army to marry before the tests could be performed.

In infants and children, where there was an open contact at home it was often necessary to maintain isolation in a hospital for the whole period. This is not always popular especially as infants often take up to eleven weeks to convert. Such segregation is necessary more for the success of the scheme than for the safety of the patient, as there is no proof that BCG does any harm to a person incubating tuberculosis.

In 1954 it was decided to discontinue giving an initial 1/10,000 Old Tuberculin Mantoux dilution followed by a 1/100 dilution if negative, and give merely a 1/1,000 dilution Old Tuberculin. The follow-up was also limited to 1/1,000 (i.e. both the six week and annual Mantoux). These changes were made because, *firstly*, time taken in giving two Mantoux tests initially was wasteful; furthermore, results had shown that undue reactions to 1/1,000 in Mantoux-positive persons were unusual. *Secondly*, the 1/100 dilution was also discontinued as some rather unpleasantly strong reactions had been noted in conversion and follow-up tests. *Lastly* there is, in fact, some considerable doubt as to the wisdom of labelling a person who reacts only to 1/100 Old Tuberculin as Mantoux positive [4]. Carroll Palmer, Director of the World Health Organization Tuberculosis Research Office, Copenhagen, calls such reactions "non-specific" and says these are caused by an unknown factor apart from tuberculosis infection [5]. Writing in the *American Review of Tuberculosis* in November 1953, he has endeavoured to prove this. Studying 22,000 nurses he found that although the numbers of "First Dose Sensitives" bears a definite relation to contact or potential contact, no such relation exists in those who are "Second Dose Sensitives," i.e. those who only react to high dose tuberculin. With the introduction of the Heaf test, however, some apparent alteration in dosage occurs to which Lieut.-Colonel Townsend will refer. Other methods of tuberculin testing such as Moro, Vollmer, &c., have the disadvantage of poor quantitative assessment.

TABLE I.—RESULTS

TOTAL NO. VACCINATED = 1,094

	Male	Female	Total	Percentage
Ulcer	156	189	345	31%
Adenitis	40	14	54	4·9%
Abscess	6	12	18	1·6%
Severe ulcer	12	9	21	1·9%
Initial conversion failure	3	7	10	0·91%

As may be seen in Table I, up to October 1955 we had vaccinated 1,094 with BCG vaccine in England. 10 failed to convert at the first attempt. 54 suffered from adenitis (4·9%). About 1 in 3 had a very small ulcer-like lesion at the site of inoculation, but only 19 could be said to be anything more than trivial. 18 developed an abscess at the site (1·6%). One nurse developed severe supraclavicular adenitis, which proved to be tuberculous. Following this, instructions were issued that injections should not be given about the insertion of the deltoid, a point also referred to by Gaisford [6].

Now what of the results in the Army from this vaccination? As in civil life in this country, it is too early as yet to assess, but I have already given you trends and indications in other countries. We have also to take into consideration the natural conversion rate of the various age groups. After 421 cases had been vaccinated we reviewed the situation and in tabulating our Mantoux results some interesting figures were arrived at.

Table II shows the percentage Mantoux positive for women of the age groups 17–22.

Table III shows the percentage from 23–30. Q.A.R.A.N.C. personnel were used entirely for these surveys as we had a wider age group to deal with.

TABLE II

Age	Total	No. positive	Percentage
17	137	86	63
18	131	86	66
19	128	90	70
20	95	71	75
21	66	52	79
22	63	55	87
Total	620	440	70

TABLE III

Age	Total	No. positive	Percentage
23	13	12	92
24	23	21	91
25	30	27	90
26	33	31	94
27	35	34	96
28	29	27	93
29	33	31	94
30	52	49	94
Total	248	232	93·5

TABLE IV.—AGE DISTRIBUTION OF SURVEY MATERIAL

Age ..	17	18	19	20	21	22	23	24	25–30	31–36	37	Total
No. ..	255	247	187	148	89	67	46	35	100	25	1	1,200

Mean Age = 19·2 years.

TABLE V.—BREAKDOWN INTO FIRST AND SECOND DOSE REACTORS

Age	Total	Pos. 0·01 mg. O.T.	Pos. 1 mg. O.T.	Negative
17–37	1,200 (100%)	510 (42·5%)	355 (29·5%)	335 (28%)

TABLE VI.—PERCENTAGES OF FIRST AND SECOND DOSE REACTORS BY AGE GROUPS

Age ..	17	18	19	20	21	22	23	24	25–30	31–36
Total pos.	151	166	135	111	69	59	38	29	85	21
% pos. ..	59%	67%	72%	75%	78%	88%	83%	83%	85%	84%

Tables IV, V and VI show the breakdown of the age distribution of the survey material and the split up of the "First Dose Reactors" and the "Second Dose Reactors". In Table VI it will be seen that the maximum sensitivity is at the age of 22. If, on the other hand we consult the percentages of "First Dose Reactors" (Table VII), we find a drop after the age of 20 to the age of 21 thereafter remaining steady (the percentage in the table being of that of the *total* reactions).

TABLE VII.—PERCENTAGE POSITIVE 0·01 MG. O.T. BY AGE GROUP (FIRST DOSE REACTORS)

Age.. ..	17	18	19	20	21	22	23	24	25–30	31–36
Total pos. ..	151	166	135	111	69	59	38	29	85	21
Pos. 0·01 mg.	69	93	86	81	41	36	23	17	51	13
%	46%	56%	64%	73%	59%	61%	60%	59%	60%	62%

The Prophit survey on geographically comparable material showed much higher percentages of first dose reactors than we did in the age groups 17, 18, 19 but after the age of 20 our figures are in agreement.

We are left wondering why first dose reactors decreased after 20, and second dose reactors therefore relatively increased. Has modern public health decreased the chance of natural immunization or is it, as Carroll Palmer suggests, that "Second Dose Reactors" are not reacting to tuberculosis at all? In which case, the total figures for Mantoux sensitivity by age groups need some revision—especially in the older ones. Why again should non-specific reactors increase in later age groups to a more or less constant level relative to the specific reactors? On the answers may well rest the value of BCG.

We have no records of any of our vaccinated personnel re-converting or reverting to Mantoux negative, but it must be realized that many have been lost sight of in civilian

life. One case, a nursing officer—BCG vaccinated successfully in June 1951—was found to have pulmonary tuberculosis in June 1954. She had worked for three months in a tuberculosis ward in Japan in 1952.

In a recent survey in the County of Sligo over a period of five years, it was found there was an average re-conversion rate of 10% though admittedly a much lower average age group is being assessed; but it gives some cause for thought and certainly we must not guarantee lifelong immunity after BCG, but we can take heart that just as contact increases the chances of conversion, so does it lessen the chances of reversion (Prophit survey).

Conclusion.—I have endeavoured to give a brief résumé of the rationale of BCG vaccination and to outline how it is used in the Army. Its value can only be assessed by time, by morbidity figures and by trends in the tuberculin sensitivity picture.

Although civilian trials are proceeding we have not so far considered the use of murine strains (Vole bacillus) in the Army.

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Lieut.-Colonel R. L. Townsend (Assistant Director of Pathology, Southern Command, and O.C. Leishman Laboratory, Aldershot):

The Heaf Multiple Puncture Tuberculin Test in Relation to the Army BCG Scheme

In its original form the Army BCG scheme depended upon the Mantoux Test, carried out in two stages, for the demonstration of negative reactors to tuberculin amongst recruits at the Depots and Training Establishments of the Royal Army Medical Corps and the Queen Alexandra's Royal Army Nursing Corps, to decide their suitability for nursing duties in contact with possibly tuberculous patients and in certain groups, regular soldiers, laboratory technicians, operating theatre technicians and radiographers for example, as an indication for BCG vaccination.

Initially the test was performed at a strength of 1 : 10,000 Old Tuberculin, the result being read after three days. Those who failed to produce a POSITIVE reaction were immediately retested at a strength of 1 : 100 Old Tuberculin, the result again being read after three days.

For a negative reactor in the specified groups, having accepted the offer of BCG vaccination, a minimum of a further three attendances at the Medical Centre was required before conversion to Mantoux positive could be obtained. This in itself is an important consideration in relation to the training programme.

With effect from April 1, 1954, this number was reduced by one attendance with the introduction of a single strength of 1 : 1,000 Old Tuberculin for the Mantoux test, both for the detection of negative reactors prior to BCG and subsequently for the confirmation of conversion to Mantoux positive and for annual follow-up.

This, however, was not considered the ideal one shot tuberculin test and at the suggestion of the Director of Pathology, War Office, in collaboration with Captain R. MacDonald, R.A.M.C., Officer in charge of the Medical Centre, Depot and Training Establishment, R.A.M.C., I carried out a trial whose object was to determine the advantages, if any, of the Heaf tuberculin test over the Mantoux tuberculin test when performed on a large scale.

Heaf tuberculin test.—The technique used was as described by Heaf (1951).

Standardized Old Tuberculin (undiluted) is "adrenalized" by adding 0·1 ml. of a 1 : 100 solution of adrenaline to 1 ml. of undiluted Old Tuberculin. A small drop of the Old Tuberculin is placed on the sterilized flexor surface of the forearm clear of superficial veins, by means of a platinum loop sterilized by flaming.

The multiple puncture apparatus, which enables six punctures to be made of equal depth (2 mm. for adults, 1 mm. for children, depending on which of the detachable endpieces is used), is sterilized by dipping the endpiece in a Petri dish containing a small quantity of spirit and passing it through a flame. When the apparatus has cooled down (about 20–30 seconds), the endpiece is pressed firmly on to the skin where the Old Tuberculin has been placed and the six needles released by the spring action. This is a painless process.

1 ml. of "adrenalized" Old Tuberculin is sufficient for approximately 200 men.

Readings.—Negative : six faint marks on the skin with no induration. Positive : Grade I, four or more indurated papules which can be felt, each measuring at least 1 mm. in diameter. Grade II: the papules have coalesced to form a ring, with normal skin in the middle. Grade III: a plateau of simple induration of any diameter. Grade IV: an area of induration on which blistering or ulceration is superadded.

Erythema is present on the third day in all cases of II, III and IV and most cases of I, but by the seventh day, only induration may be present.

Mantoux tuberculin test.—As a routine 0·1 ml. of 1 : 1,000 Old Tuberculin is injected intradermally into the sterilized skin of the flexor surface of the forearm so as to raise a wheal of at least 5 mm. diameter. A positive result gives an area of induration of not less than 6 mm. in diameter when read on the third day. Simple erythema is not regarded as a positive reaction.

Purified Protein Derivative (P.P.D.) may be substituted for Old Tuberculin in either test in which case the P.P.D. need not be "adrenalized" in the Heaf test.

Heaf-Mantoux Comparative Trial

Method.—Each subject received a Heaf test in the left arm and a Mantoux test using 1 : 10,000 Old Tuberculin in the right arm. Three days later the Heaf results were read with the right arm concealed. Then the Mantoux results were read with the left arm concealed. Those subjects who gave a reaction of 0–2 mm. induration with the Mantoux test were re-tested with 1 : 100 Old Tuberculin, and those who gave a reaction of 3–5 mm. induration, with 1 : 1,000 Old Tuberculin. The Heaf results were read again four days later (the seventh day after Heaf testing), as were the results of the 1 : 100 and 1 : 1,000 Mantoux tests.

Results.—Total number of men tested (Mantoux and Heaf): 640.

Mantoux Positive		Heaf Positive, third day	Heaf Positive, seventh day
1 : 10,000 ..	130	129 (99·23%)	128 (98·46%)
1 : 1,000 ..	59	59 (100%)	59 (100%)
1 : 100 ..	178	157 (88·20%)	169 (94·94%)
Totals	367	345	356
Negative		**Positive, third day**	**Positive, seventh day**
1 : 1,000 ..	3	2	2
1 : 100 ..	270	8	12
Totals	273	10 (3·66%)	14 (5·13%)
Totals	640	355 (*a*) (55·47%)	370 (*b*) (57·81%)

(*a*) Heaf - positive on third day, Heaf-negative on seventh day	7 (1·86%)
(*b*) Heaf - negative on third day, Heaf-positive on seventh day	22 (5·83%)
Total Heaf-positive (on one or both days) ..	377 (58·9%)

Discussion

Before attempting to draw conclusions from the above results, it is necessary to point out two possible sources of error. First, measurements of the diameter of induration in the Mantoux tests were made with a ruler. Secondly, there were 22 (5·83%) instances where the Heaf readings were negative on the third day but had become positive by the seventh day. All these had received 1 : 100 tuberculin on the third day, and it has been suggested that this had "potentiated" the Heaf test to make it positive by the seventh day.

In an effort to resolve this latter problem, 304 men were Heaf tested and received no Mantoux test. This survey gave the following results:

Total number of men tested	304
Heaf-positive on one or both days	161 (52·96%)
Heaf-positive on third day	151 (49·67%)
Heaf-positive on seventh day	158 (51·97%)
Heaf-negative on third day, Heaf-positive on seventh day ..	10 (6·21%)
Heaf-positive on third day, Heaf-negative on seventh day ..	3 (1·86%)

These figures follow closely those obtained in the main trial, and despite the small number investigated they do suggest that there is in fact no potentiation of the Heaf test when a second Mantoux test is performed on the third day. It is inferred from these facts that the third day is too early to read the Heaf test and that the fifth day would be better.

It is to be expected that those men who are Mantoux-positive to the higher dilutions of tuberculin (1 : 10,000 and 1 : 1,000) will give a high percentage of Heaf-positive readings on both third and seventh days, since their tuberculin sensitivity is high. This is borne out by the results.

The percentage of Heaf-positives amongst those who required 1 : 100 tuberculin to reveal sensitivity was appreciably lower, being 88·2% on the third day and 94·94% on the seventh. The higher percentage of Heaf-positives on the seventh day has already been discussed.

The percentages of total Mantoux- and Heaf-positives (57·34% and 58·9%) are very similar but both figures are much lower than the 85% usually quoted for the population as a whole. This is no doubt due to the age group involved, chiefly 18 to 21 years.

Advantages of the Heaf Test

(1) *Speed.*—If two instruments are available and used alternately, one being allowed to cool after sterilization while the other is in use, 200 tests can be performed in one hour by one operator. The same number of Heaf readings can be done in a much shorter time, depending on the supply of clerks to write down the results.

(2) *Simplicity.*—If the quantity of tuberculin is sufficient, and if the apparatus is placed firmly and squarely on the forearm, the performance of the test is uniform and foolproof. No skill is required.

(3) *Painlessness.*—The Heaf test is painless.

(4) *Accurate and easy readings.*—As soon as one is familiar with the Heaf-positive Grade I results, the readings are more easily and speedily performed than Mantoux readings. The reading of Grades II, III and IV is especially simple.

(5) *Lack of severe reactions.*—A small number of men with Grade IV readings complained of slight discomfort which cleared up quickly with Anthisan cream. It must be stated, however, that painful arms following Mantoux testing have been equally uncommon in this unit.

In a small proportion of dark swarthy types (less than 1 in 60), there occurred at the site of puncture, an intense staining which persisted. This might constitute a disadvantage in women.

Summary

(1) The Mantoux and Heaf tuberculin tests have been compared in 640 men.

(2) The results of the Heaf tests closely follow those of the Mantoux tests, and therefore the Heaf test may be substituted for the Mantoux.

(3) It is suggested that the fifth or sixth day would be more suitable for reading the Heaf test than the third day.

(4) The Heaf test is simple and the results are easily read.

(5) The Heaf test is painless and the reactions are negligible.

As a result of these findings it was decided to take the Heaf tuberculin test into more general use in the Army.

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Captain T. M. Robinson:

BCG Inoculation and the Problem of Tuberculosis in Gurkha Troops

Mantoux testing and BCG immunization of Gurkha recruits was commenced in January of 1952 at the Brigade of Gurkhas Depot at Sungie Patani in Malaya. Over the period 1952 to 1954, 2,044 recruits were Mantoux tested and those negative to 0·1 ml. of 1/100 Old Tuberculin were inoculated with BCG by intradermal injection.

The BCG which was used was the Pasteur Institute freeze-dried product. This makes up for use quite easily by adding the provided diluent when a homogeneous emulsion forms which is perfectly simple to use. Up to the time of use the BCG was kept in a refrigerator at 4° C. in the dark. Afterwards testing for Mantoux conversion was carried out with 0·1 ml. of 1/100 Old Tuberculin at eight-week intervals. Those recruits in whom conversion had not occurred by the end of twenty-four weeks were reinoculated with BCG. In all of this Mantoux testing, readings were made at forty-eight hours and, in the case of doubtful reactors, again at seventy-two hours. The minimal positive reaction was taken as an area of induration measuring 7 mm. in diameter.

The Mantoux conversion results from the freeze-dried BCG were at first poor, and this necessitated reinoculation in a high proportion of the cases. With improvements in the general technique and the observation of certain necessary precautions in the use of freeze-dried BCG, the conversion rate at present obtained is in the neighbourhood of 99% at seventeen weeks, a result comparable to that obtained with "fresh" BCG in Europe.

The points which were observed, and which underlie the development of the technique which is now used were as follows:

(1) The BCG which is used must be given well within the expiry dates stated by the manufacturers. There seems to be a good deal of variation in batch potency with age. The first batch used produced a conversion of only 18·9% at seven weeks after inoculation, and 48·9% at sixteen weeks after inoculation. The next batch used, which was, in contrast, injected well prior to its official expiry date produced conversion of 77% at eight weeks after inoculation.

(2) The use of larger doses of vaccine. In 1953 for a period the effect of a double dose of vaccine was studied. The conversion rates were higher than the overall rates produced

by the first inoculations of single doses used in early 1952—namely, 61·5% at fourteen weeks as compared with 48·9% at sixteen weeks. (Once again batch variation was noticed as one batch produced only a 58% conversion on 269 men at fourteen weeks and a second batch 74% conversion on 66 men at the same time.) There were no complications observed as a result of the use of this high dosage of BCG. This method was dropped, however, and the single dose resorted to again when the next factor was realized. This, probably the most important of all, was the avoidance not only of temperature alteration to the vaccine, which had been carefully observed up to then, but also its complete protection from both direct and indirect sunlight. This latter, the so-called "skyshine", is intense in Malaya, even indoors, and protection of the vaccine against it resulted in a great improvement in the Mantoux conversion results. This protection necessitated not only the preservation of the vaccine in the dark until use, but its reconstitution in a darkened place and the use of syringes "blacked out" with opaque material for the administration of the vaccine.

With the precautions against heat and skyshine, the conversion rate last year rose to 89·4% at seven weeks and 99·6% at seventeen weeks.

To summarize: The freeze-dried vaccine must be treated with great respect in the tropics to obtain good Mantoux conversion results; it must be scrupulously protected against heat, and from exposure not only to direct sunlight but also to skyshine. It should also be used well within the expiry limits stated by the manufacturer.

Results, so far, of the BCG inoculation: 989 Gurkha recruits had been given BCG from the period January 1952 up till 1955. 1,055 recruits were Mantoux positive on their arrival in Malaya and were not given BCG.

Out of the inoculated group of 989—3 cases of pulmonary tuberculosis have developed over this three-year period; out of the uninoculated group of 1,055, 16 cases have developed over the same period. That is, over five times as many cases have developed in the uninoculated as in the inoculated group.

It must be emphasised that all of these men were passed as having clear chest X-rays on the M.M.R. taken within a few weeks of their arrival in Malaya and that the cases presented, or were diagnosed, as having tubercle on an average of eight months after their arrival in Malaya.

This being so, the possibility that many or all of the 16 men with tubercle in the uninoculated group were developing or had developed tuberculosis at the time of the original Mantoux testing, becomes a remote one. The results are therefore, so far, good.

Of equal interest, and certainly of wider importance as far as the Gurkhas themselves are concerned, are facts which came to light during the Mantoux survey of the recruits and during the actual treatment of Gurkhas with established tuberculosis at the British Military Hospital, Kinrara.

It has for a long time been held that Gurkhas, as a race, are a "primitive" people with regard to tuberculosis and subject to the disease in a lethal "primitive" form.

The term "primitive tuberculosis" as applied to a race, means a people which has had little contact with the disease over the centuries, and hence little opportunity to build up native resistance by repeated contacts with the disease. As applied to the individual it means the likelihood of the development of an acute, rapidly fatal disease with rapid blood-borne and lymphatic dissemination.

This concept has been applied to Gurkhas for two main reasons. The first is that until the last four years there has been no organized sanatorium treatment for them; men with the disease were discharged from the Army and returned to Nepal where no means of treatment existed and where many did in fact die of the disease, sometimes quite soon after their return. This was well known to the soldiers, so much so that a discharge from the Army with tuberculosis had come to be regarded by the men as tantamount to a death sentence. In 1908 a published survey of Tuberculosis in the Indian Army (Johnston, 1908) showed the Gurkhas as possessing the highest incidence of tuberculosis amongst the caste regiments. It must be pointed out that little follow-up of cases was possible at that time; that diagnosis was made largely upon clinical grounds alone, and that post-mortem examinations of fatal cases were seldom performed. It has also been stated that acute and rapidly fatal forms of tuberculosis with widespread blood-borne disease are often found in Gurkhas (Aspin, 1947).

This impression of the gravity of the disease, formed first at the beginning of the century, has gained a firm foothold not only amongst those concerned with the medical care of Gurkha soldiers, but amongst the troops themselves, their dependants in Nepal and the inhabitants of our recruiting areas.

Additional, and very powerful, support for the concept came from a Mantoux survey which was carried out in 1944 at a recruiting depot in India (Aspin, 1947) amongst newly arrived recruits and battalion riflemen from West and Central Nepal. This work was done upon troops in transit, and for this reason a single dose Mantoux method had to be used.

using 0·1 mg. of Old Tuberculin, and one-third of the cases had to be examined at only thirty-three hours instead of the forty-eight hour and seventy-two hour readings which it was possible to undertake in the remainder. It was stated, using this method, that a very high proportion of the recruits arriving from Nepal were Mantoux negative; an average of 23·2% only were Mantoux positive.

A finding of this sort is extremely important, since owing to geographical, quite apart from political, considerations, little or no accurate information about the amount of tuberculosis in Nepal can be obtained directly and only an indirect method such as a Mantoux survey can afford a means of approaching the problem.

The findings of this 1944 survey, therefore, that a very high proportion of young recruits were Mantoux negative, gave added weight to this concept of the Gurkhas as a primitive people with regard to tuberculosis, and of course it agreed well with the established ideas about the disease in these troops.

So much for past information.

The information gained both from the recent Mantoux survey and also from the study of established cases of tuberculosis shows that the concept of "primitive" tuberculosis as applied to the Gurkha seems to be erroneous and that in this respect the problem of Gurkha tuberculosis has been exaggerated.

In the Mantoux testing of 2,044 recruits, 90·8% of whom were in the 15–19 year age group, no less than 51·1% were Mantoux positive—that is, more than twice the number reported in the 1944 survey. The recent survey was admittedly performed upon recruits at a time varying from five to eight weeks after they had actually left Nepal as distinct from the previous survey when they were examined straight from the hills. It does seem unlikely, however, that such large numbers would undergo natural Mantoux conversion in this short time. A much more likely explanation of the differences in the results between the surveys lies in the fact that a more thorough and prolonged investigation has been possible recently in Malaya with the use of both 0·01 and 1 mg. of Old Tuberculin in testing and with readings being made in all cases at forty-eight and seventy-two hours.

From these Mantoux results it thus seems that contact with tuberculosis in Nepal seems to occur to about the same extent that obtains in at all events the rural areas of India and Europe.

The Gurkhas cannot therefore on these grounds be labelled a primitive people with regard to tuberculosis, nor indeed do the cases of tuberculosis which develop conform in any way to a primitive pattern.

The clinical information is based upon a study of 140 cases of pulmonary tuberculosis treated by Capt. K. A. Manley at the Gurkha Sanatorium at Kinrara during 1951–1953. He found that of these cases, 93%, that is 130, presented the appearances of ordinary "reinfection" or "adult" fibrocaseous pulmonary tuberculosis. The other 10 cases comprised 8 pleural effusions and 2 cases with primary complexes. There were no cases which deteriorated rapidly to a fatal termination with acute pulmonary lymphatic and hæmatogenous dissemination such as is described in so-called "primitive" peoples with regard to tuberculosis. In fact, over 1951–1953 there were no deaths at all in the sanatorium, this among patients whose lesions varied from minimal ones to extensive bilateral disease with cavitation. It cannot be argued that the development of this mythical acute fatal disease was hindered by the use of chemotherapy because chemotherapy was not used at all in 44% of the series, that is 62 men. (Of these 62 men, 33 were actually discharged with quiescent lesions in 1953.) In the same way collapse therapy was not used until the disease in any patient had settled after bed rest, so that this cannot be invoked as a disturbing factor.

Both clinically and radiologically the lesions in these patients resembled those seen in Europeans and the response to treatment so far has been similar to that found in European communities. It is a reasonable conclusion that the Gurkha's racial immunity is also comparable to that of Europeans; there has been found to be no clinical ground for regarding the Gurkhas as a race which has little resistance to tuberculosis.

The Hill people of Nepal appear broadly to arise from two root sources. The first of these is predominantly Indian migrating particularly into the West, the other more Mongolian in appearance and physique, migrating mainly into the East. Both of these peoples have a long acquaintance with tuberculosis and it seems not unreasonable to suppose that tubercle in Nepal has at least as long a history as it has in other Asian countries. This is certainly suggested by the Mantoux findings in new recruits, by the type of disease which is encountered, and by the resistance to tuberculosis and the response to treatment shown by patients with the disease.

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Section of Experimental Medicine and Therapeutics

President—E. E. POCHIN, M.D., F.R.C.P.

[*December* 13, 1955]

DISCUSSION ON RENAL BIOPSY

Dr. Robert C. Muehrcke, Dr. Robert M. Kark, Dr. Conrad L. Pirani and Dr. Victor E. Pollak (read by Dr. Muehrcke):

Renal Biopsy—Technique and Clinical Application[1, 2]

Iversen and Brun (1951) introduced a method of percutaneous renal biopsy with the patient sitting upright. Although their method was safe, adequate renal tissue for histological diagnosis was obtained in only a small percentage of attempts. Kark and Muehrcke (1954) reported a modified technique of needle biopsy of the kidney with the patient in the prone position. This procedure is safe, usually painless to the patient and representative samples are obtained in a high percentage of attempts. In brief, a sandbag under the abdomen fixes the kidney against the back and provides hæmostasis through pressure after biopsy. The biopsy site in the lower pole of the right kidney is located by X-ray and the aid of a fine atraumatic exploring needle. The kidney is located when the exploring needle moves through a wide arc with respiration. The biopsy specimen is extracted with a modified Vim-Silverman needle (Fig. 1).

FIG. 1.—The atraumatic exploring needle and the three parts of the biopsy needle, the obturator, the outer sheath and the cutting prongs.

The safety of the procedure depends on careful selection of patients, meticulous pre-biopsy studies and a careful post-biopsy follow-up. The contra-indications to renal biopsy are: an uncooperative patient, patients with a bleeding tendency, or with one kidney, or with renal neoplasm or large cysts, and patients with oliguria and a blood urea above 100 mg. per 100 ml. of blood, which is rising. Preliminary studies before biopsy should include urine culture and examination, studies of the coagulation mechanism, X-ray of the kidneys, tests of renal function, and biochemical analysis of the blood—especially blood urea. These studies can be done on an outpatient basis, but the patient must always be admitted to hospital for the renal biopsy. This rule must never be relaxed.

Over one thousand renal biopsies have been done (Iversen *et al.*, 1954; Parrish and Howe, 1955; Joske, 1954; Muehrcke *et al.*, 1956; Jackson *et al.*, 1955). There have been no deaths and morbidity was slight. The main advantage of renal biopsy in clinical practice is that it provides an exact histological picture on which the physician can base his diagnosis, treatment and prognosis. Renal biopsy is an efficient clinical tool in the management of patients with general medical disease of the kidney. It is especially valuable in patients with the nephrotic syndrome (*see* Figs. 2 and 3), hypertension (*see* Fig. 4), amyloidosis, diabetes, so-called collagen diseases, toxæmia of pregnancy, anuria (*see* Fig. 5), hyperparathyroidism and unexplained proteinuria.

Cultures of renal blood and tissue are useful in isolating organisms from within the kidney. 5 patients were observed in whom urine specimens were repeatedly sterile. They all had proteinuria but no chills, sweats, burning on urination, back pain or pyuria (Table I). Cultures of their kidney biopsies were positive. All 5 patients responded very well to antibiotic therapy and renal function was restored to normal. There was marked improvement of the post-therapy renal histology (*see* Figs. 6 and 7). At present this condition cannot be recognized except by renal biopsy. Muehrcke *et al.* (1955*a*) have termed this disease "subacute bacterial nephritis".

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[2]Support in part by grants from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland (H. 1029) and from Eli Lilly and Company.

TABLE I.—CLINICAL DATA "SUBACUTE BACTERIAL NEPHRITIS"

Patient	Fever	Back pain	Proteinuria	Hæmaturia	Pyuria	Leucocytes/ c.mm.	Organism from kidney
M. P.	0	0	Trace	0	0	8,500	*Staph. aureus.** Coag. pos.
W. D.	0	0	Trace	0	0	6,500	*Strep. fæcalis*
J. B.	0	0	Trace	+	0	11,500	*Staph. albus.* Coag. pos.
P. T.	+	0	4+	+	0	9,600	*Strep. fæcalis**
F. C.	0	0	4+	0	0	12,700	*E. coli**

*Post-biopsy urine culture had identical organisms as in kidney.

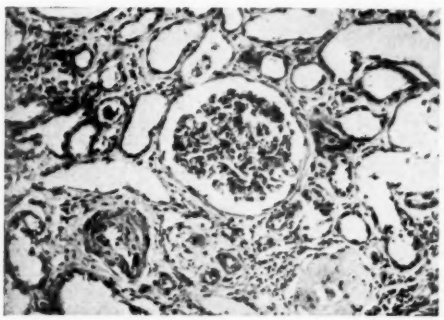

FIG. 2.—Renal biopsy from hypertensive male aged 74 years, showing normal glomeruli, interstitial œdema and severe tubular degeneration. Following myocardia infarction in 1954, there were recurrent episodes of congestive cardiac failure. After prolonged mercurial diuretic therapy, an apparent Ellis type II nephrotic syndrome developed. Two months later renal biopsy showed the above picture which may be due to the mercurial therapy. (H. and E. ×92.)

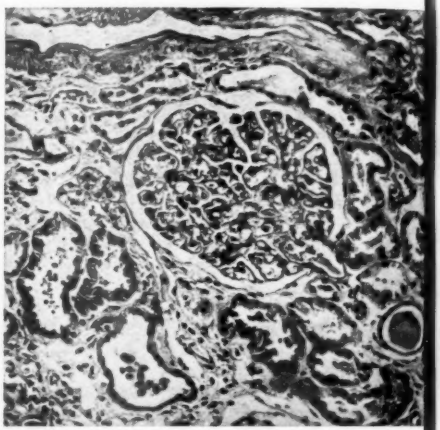

FIG. 3.—Renal biopsy, from a man aged 50 years with the nephrotic syndrome, showing Ellis type II nephritis. In view of a two-year history of bronchiectasis and a high γ-globulin peak on the serum electrophoretic pattern, secondary amyloidosis was suspected. Note the thickened glomerular basement membrane and the interstitial œdema. (H. and E. × 142.)

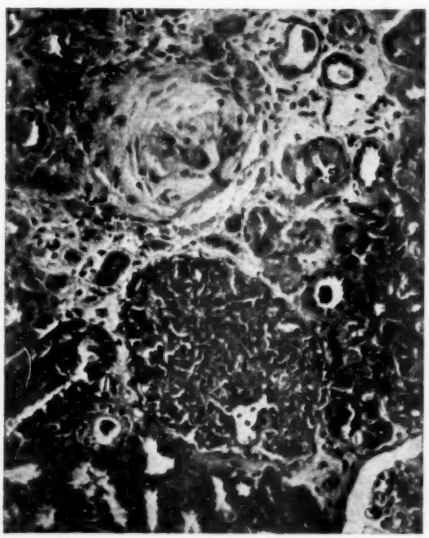

FIG. 4.—Biopsy taken from a hypertensive male aged 51 years, with early sign of renal failure, but normal blood urea. Clinically a primary pyelonephritis was suspected but biopsy showed severe nephrosclerosis. This case illustrates how renal biopsy may change the clinical diagnosis. (H. and E. × 135.)

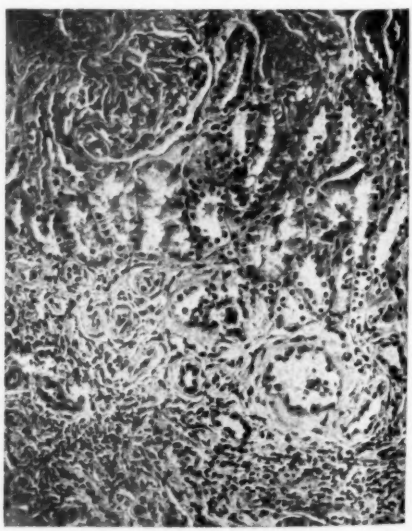

FIG. 5.—Renal biopsy from a 29-year-old woman with a slightly impaired renal function. Eight months previously toxæmia of pregnancy and premature placental separation had been followed by oliguria, with diuresis on the eleventh day. There is sharp delineation of scarred from healthy tissue confirming the clinical diagnosis of focal bilateral cortical necrosis. (H. and E.) ×125.)

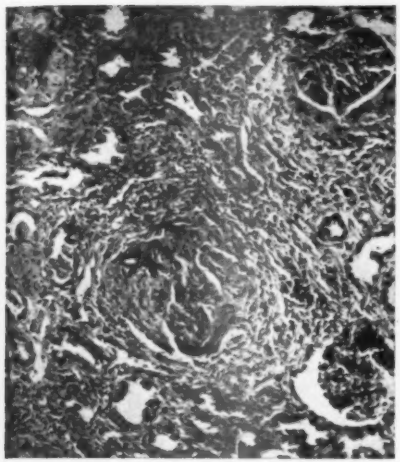

FIG. 6.—Renal biopsy taken from a 23-year-old male with "subacute bacterial nephritis". A pure culture of *Streptococcus fæcalis* sensitive to tetracycline was grown from the renal tissue. Note the marked hypercellularity and ischæmia of glomeruli, which are compressed by large crescents. There is interstitial œdema with foci of chronic inflammatory cells. (H. and E. × 85.)

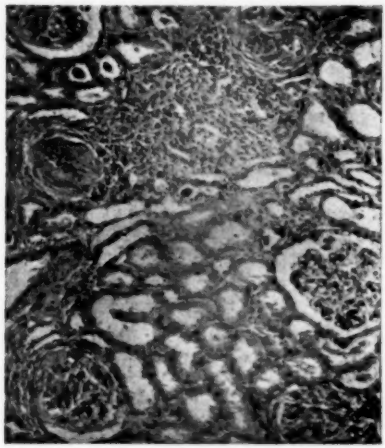

FIG. 7.—Post-therapy biopsy of patient P. T., taken four months after therapy with tetracycline. Note both the hyalinized glomeruli and the apparently normal glomeruli. (H. and E. × 85.)

Serial renal biopsy is an ideal method for studying the histological evolution of kidney disease, for studying the effects of hormones and drugs on the cardiovascular system, and for studying reversible lesions within the kidney. Renal biopsy is useful in cytochemical and electron microscopic studies of kidney disease. In addition to changes occurring in the nephrons itself, histological examination provides information on changes in the blood vessels and the ground substance. Therefore, vascular diseases, such as hypertension, and diseases of reaction, such as systemic lupus erythematosus, can be followed.

The natural history of renal lesions in systemic lupus erythematosus was studied by serial biopsies (Muehrcke *et al.*, 1955*b*). The glomerular lesions developed in two distinct ways. In the first, a local glomerulitis appeared, became generalized, and then developed into a subacute glomerulonephritis with epithelial crescents, indistinguishable from an Ellis type I nephritis. The second began as an irregular thickening of the glomerular "basement membrane" and sometimes progressed via a membranous glomerulonephritis ("wire-loop lesions") to a similar subacute glomerulonephritis picture. When local or generalized glomerulitis was present, leucocytes and leucocyte casts were found in the urine. Mild proteinuria was noted in patients in a severe general glomerulitis stage of lupus nephritis. Moderate cylinduria and impairment of renal function were associated with subacute glomerulonephritis. Hypertension, marked renal impairment, azotæmia and a fixed urinary specific gravity accompanied the chronic glomerulonephritis stage of lupus nephritis. Observations of the clinical course of systemic lupus erythematosus and data from serial renal biopsies indicate that cortisone was completely without either beneficial or adverse effect on the kidney lesions.

Because serial renal biopsy is useful in the study of recoverable lesions, the renal lesions of pre-eclampsia were investigated (Pollak *et al.*, 1955). During toxæmia of pregnancy, the glomerular capillaries appeared swollen, œdematous and smudgy and non-specific tubular degeneration was present. After the blood pressure had returned to normal and œdema and proteinuria had subsided, subsequent biopsies failed to show these lesions. Renal tissue cultures in these cases were usually sterile.

Renal cytochemical studies indicated a reduction of alkaline phosphatase, but a normal concentration of esterase in the proximal tubules of patients with the nephrotic syndrome.

In studying the problem of proteinuria, renal biopsies have been done on a number of patients whose urine had been consistently free of protein. In some of these patients, proteinaceous material was readily seen in Bowman's space. Patients with gross proteinuria showed proteinaceous material in the tubular lumen and, in most cases, also in Bowman's space (Muehrcke *et al.*, 1954). These observations confirm the concept that protein is filtered by the glomerulus and is reabsorbed by the tubules.

In conclusion, the authors express themselves as a group of optimistic enthusiasts. Ten

years from now, we believe our understanding of the intimate pathophysiology of the nephron will be advanced to a remarkable degree by virtue of serial renal biopsy studies. In closing, a word of caution. *Although renal biopsy is a most valuable, practical, clinical tool, it is not an office procedure.*

The safety of the patient depends on careful selection, meticulous pre- and post-biopsy care; and the skilful manipulation of the biopsy needle by an interested physician.

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Dr. R. A. Joske (The Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital, Melbourne, Australia):

Dr. Muehrcke has already discussed the technique of renal biopsy, and its use in the study of the nephrotic syndrome and systemic lupus erythematosis. I shall devote my time chiefly to discussing the use of renal biopsy in the study of the renal lesions occurring in diabetes mellitus.

Regarding technique, there are now published reports concerning some hundreds of renal biopsies, chiefly from Scandinavia and the United States. It appears from these that renal biopsy, if performed by a trained operator with due regard to the patient's renal status and hæmostatic capabilities, is both a safe and feasible method of investigation. In Melbourne, in over 100 attempted or successful renal biopsies, we have obtained adequate tissue for histological diagnosis in about 70% of attempts. None of our patients has suffered more than transient discomfort or hæmaturia; certainly none has required blood transfusion or surgical intervention, and none has died as a result of renal biopsy.

Our knowledge of the fine structure of the normal human kidney is very imperfect. Only recently have the electron microscopic studies of Hall (1955) and of Rinehart (1955) cleared our minds as to the existence of the glomerular mesangium. It now seems that both glomerular epithelium and endothelium are directly adjacent to a single inner basement membrane which is porous and probably derived from the endothelium.

Some classical views on the regular well-defined "brush border" of the proximal convoluted tubules are also not in accord with the appearances seen in rapidly fixed fresh biopsy material. In such material Raaschou and his colleagues (1954), and we in Melbourne, have regularly noted a frayed, "granulated" appearance of the inner borders of these cells. This has been shown by Oliver and his associates (1954) to be associated with protein resorption from the glomerular filtrate. The biopsy specimens thus provide some anatomic evidence that filtration and resorption of protein occurs normally in the human kidney.

A further point of interest is the presence in about 10% of biopsies of tall regular columnar epithelium in the cells of Bowman's capsule (Finckh and Joske, 1954). This well may be a normal occurrence and related rather to functional activity than to pathological change.

An undoubted future use of renal biopsy in the study of the kidney will be the investigation of specific tubular enzymes under various normal and pathological circumstances. This has already been done with liver enzymes in liver biopsies by Dale (1953). Bjørneboe and his co-workers (1952) have studied the distribution of alkaline phosphatase in renal biopsies using Gomori's method, but there is little other published work in this field.

Our experience with renal biopsy in the nephrotic syndrome is not great, but our findings agree with those of Bjørneboe *et al.* (1952) and with those of Dr. Muehrcke and his colleagues in emphasizing the histological diversity that underlies the clinical and biochemical unity of the nephrotic syndrome. Our biopsies from patients with simple or complicated nephrosis have shown such varied pictures as progressive Type I nephritis, Type II nephritis, renal amyloidosis, systemic lupus erythematosus, diabetic glomerulosclerosis, and normal renal tissue. The differing therapeutic and prognostic implications of these differing lesions require no further comment. But in some instances this information may be attained only by renal biopsy.

Of systemic lupus erythematosus (S.L.E.) I would make only two points. The first is the frequency of renal lesions in this disease, even in the absence of clinical evidence of lupus nephritis (Joske and Stubbe, 1956). We have found demonstrable renal lesions by biopsy

in all of 13 patients investigated by this method, though the changes vary in degree from one patient to another. The second point is that renal lesions may develop in S.L.E. despite continuous and apparently adequate cortisone therapy. We have now studied 2 patients, both of whom initially presented neither clinical nor histological evidence of renal involvement. Both have been maintained on a dose of cortisone which produced good symptomatic relief; but in both serial biopsies have shown the development of a moderately severe lupus nephritis (Taft, 1955).

Our greatest experience with renal biopsy has been in the study of the renal changes associated with diabetes mellitus (Taft, Finckh and Joske, 1954), and I wish to discuss this in more detail. The present results are based upon the first 50 successful renal biopsies performed upon diabetic patients.

Five types of lesion can be distinguished in diabetic kidneys: nodular glomerular lesions (Kimmelstiel and Wilson, 1936); diffuse glomerular lesions (Bell, 1950); exudative lesions (Fahr, 1942; Koss, 1952; Barrie *et al.*, 1952); non-specific vascular lesions; and infective changes. The latter may be dismissed briefly. They are clearly related to ketosis (Dubois, 1953) and are patchy in their distribution so that they are poorly studied by renal biopsy as has been shown by Brun *et al.* (1953) in diabetics and by Kipnis *et al.* (1955) in non-diabetic pyelonephritis.

The nodular and diffuse lesions appear to be related. Both occur in older patients with a long history of diabetes mellitus, and histologically using a number of staining techniques there appears to be a transition from one type to the other. We have not yet seen nodular glomerulosclerosis in non-diabetics or in young diabetics, though this has been reported in the literature.

The exudative lesions differ in several respects. They occur not only in the glomerular tufts, but also on Bowman's capsule. Histologically, exudative lesions are PAS positive and probably contain lipid. Similar material is often seen also in juxta-glomerular arterioles. They can be distinguished from nodular and diffuse lesions by both connective tissue stains and the PAS method. They occur frequently in younger patients, and are often the first histological evidence of diabetic renal disease.

The non-specific vascular lesions are not remarkable. They occur mainly in older patients and do not seem to differ from atheroma in non-diabetics.

These various types of lesion may readily be distinguished in renal biopsies, and it is possible by means of renal biopsy to define the type or types of change present in each case, although one biopsy may of course show more than one type of lesion. Of our first 50 patients, the biopsy was within normal limits in 21, showed non-specific vascular or ischæmic changes only in 10, and showed diffuse, exudative or nodular changes in 19. These results may be related to the clinical findings.

The average age of the 21 patients with normal biopsies was 29 years (range, 14 to 65 years), the average known duration of their diabetes was five years, only 4 were hypertensive, only 3 had retinopathy, and only 3 at any stage have shown elevation of the blood urea above 40 mg.%. None had proteinuria.

These figures contrast sharply with the other two groups.

The average age of the 10 patients with non-specific vascular disease was much higher, being 54 years (range, 33 to 77 years), and the average duration of their diabetes was longer, thirteen years (range, four months to twenty-six years). 8 of the 10 were hypertensive, 9 had either hypertensive or diabetic retinopathy, 3 had proteinuria and 3 diminished renal function.

The 19 patients with specific diabetic renal disease were intermediate. Their average age was 45 years (range, 14 to 71 years), the average known duration of their diabetes was eleven years (range, three weeks to twenty-one years), 13 were hypertensive, 8 of 14 whose fundi were examined at the time of biopsy showed diabetic retinopathy, 11 had albuminuria, and 12 diminished renal function.

This group of patients includes 5 from whom definite evidence of diabetic nephropathy was obtained by renal biopsy in the absence of any other evidence of renal disease. These were young patients, and the presence of renal disease in these biopsies was quite unexpected. Thus, a boy of 17 years, with a diabetic history of only three weeks, a blood-pressure of 125/75 mm.Hg, no albuminuria and no retinopathy showed on biopsy unmistakable diffuse and exudative lesions, and, despite his age, one sclerosed glomerulus (Taft and Joske, 1954).

Assessment of therapeutic control of diabetic hyperglycæmia is difficult, so that our classification of the present 50 cases into four groups—"good," "fair," "poor" and "unknown"—can only be an approximation. It is based on clinical observation and on random blood and urine sugar estimations both in the wards and out-patient department. The relation between control as thus assessed, and the results of renal biopsy are shown in Table I. There is little correlation between them, but the numbers are small and further study is obviously necessary.

TABLE I.—RELATION OF HISTOLOGICAL FINDINGS TO CONTROL OF HYPERGLYCÆMIA IN 50 DIABETIC PATIENTS STUDIED BY RENAL BIOPSY

Biopsy results	Control of hyperglycæmia			
	Good	Fair	Poor	Unknown
Normal	3	6	7	5
Non-specific vascular disease ..	3	4	2	1
Diabetic renal disease	3	11	5	0

Finally, what is the significance of renal biopsy in diabetes mellitus? Firstly, it is only by biopsy methods that it is possible to study serially the natural evolution of diabetic renal disease, and its relation to biochemical and therapeutic measures. Secondly, the problems of diabetic vascular disease are of increasing importance in the management of the diabetic patient, and it is only by renal biopsy that these changes may be given a precise pathological basis in any particular case. This point may well be of considerable therapeutic importance in the light of recent reports of the effects of hypophysectomy (Luft *et al.*, 1955) and of adrenalectomy in an otherwise progressive and fatal disease.

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Dr. H. E. de Wardener and Dr. M. Hutt:

We have been doing renal biopsies for about nine months and the following is a short account of the difficulties we have encountered and our results.

From the patients' point of view a renal biopsy appears to be as painless as a well-conducted liver biopsy but for the person performing the biopsy it is a much more difficult procedure. Localization of the kidney, by watching for the swing of the needle with each respiration is relatively easy, though in the obese this may be misleading, for the needle may swing when it is in the perirenal fat. The greatest difficulty is obtaining a specimen of suitable size from the cortex; occasionally the sample may consist only of tubules or it may be so small as to give little information. We have attempted a renal biopsy on 40 occasions and obtained 30 specimens; of these two consisted of tubules only.

Microscopical hæmaturia invariably follows renal biopsy but in 2 of our patients there was gross hæmaturia with clot colic. One of these was suffering from hypertension and it seems from discussion with others who are performing renal biopsies that gross hæmaturia is more likely in such patients (Corcoran, 1955, personal communication). As a result we now make certain, by the use of hypotensive drugs if necessary, that the diastolic pressure is not higher than approximately 100 mm.Hg, during and for a few hours after the biopsy. The other patient was suffering from myelomatosis, he had a normal blood pressure and the bleeding, clotting and prothrombin times were normal and there was also a normal number of platelets; the blood urea was 150 mg.%. But on the day after the biopsy it was noted that there was minimal bleeding from the gums. It is obvious that such a sign should be particularly looked for and if present renal biopsy should not be performed, and it would also seem wise to include a tourniquet test before the biopsy. Immediately after the biopsy we now give a large drink of water, for the diuresis which follows allows an early estimate to be made of the extent of the hæmaturia which has been caused, and also diminishes the likelihood of clot formation; we also have an impression that it may diminish the amount of hæmaturia. Dr. Muehrcke and his group also give a drink of water for much the same reasons. The information which can be obtained from renal biopsy can either help to establish the diagnosis or to clarify the natural history of the structural changes which occur in renal disease. We have been able to make a diagnosis on three occasions when other methods had been unsuccessful. Renal amyloidosis was found in one patient with a nephrotic syndrome and a normal liver biopsy; necrotizing glomerular capillaritis led to a diagnosis of polyarteritis nodosa in another patient with an illness resembling acute nephritis; and nephrocalcinosis was found in the third patient who was suffering from a peptic ulcer and a raised blood urea.

Section of Neurology

President—REDVERS IRONSIDE, F.R.C.P.

[*November* 3, 1955]

[Continued from May *Proceedings*, p. 308]

Attacks of Orthostatic Hypotension Resembling Focal Epilepsy Associated with Diabetes and Hypoparathyroidism.—R. HIERONS, M.R.C.P., and J. SHELDON, M.B., B.S.

Mrs. E. J., aged 45, was admitted to King's College Hospital under Dr. S. Nevin. Over the previous five years there had been loss of weight, lassitude and an increasing slowness in walking with unsteadiness and numbness of the feet and fingers. Aching pains in the legs, diarrhœa and occasional rectal incontinence were present during these years. The patient had experienced for the last two years, several times daily, attacks of loss of consciousness preceded by involuntary turning of the head to the left. She was seen during some of these attacks to become rigid and occasionally had injured herself and been incontinent.

At the age of 22 a thyroidectomy had been performed, followed by loss of phonation lasting several years and for the next ten years frequent attacks of tetany. These attacks were stopped by drinking large daily quantities of milk. The diagnosis of diabetes mellitus was established at the age of 32. For some years, however, her diet and insulin requirements had been neglected.

Abnormal physical findings consisted of a slight degree of dementia. Speech was indistinct due to bilateral abductor paralysis of the vocal cords. Exophthalmos, ptosis and lens opacities were present on both sides. Examination of the motor system revealed slight weakness in the upper limbs confined to the extensor muscle groups and moderate weakness of the flexor muscles of the lower limbs—most severe distally. Reflexes were feeble in the arms and absent in the legs including no response from plantar stimulation. The only sensory defect in the upper limbs was in two-point discrimination (occasional errors at 6 mm. over the finger tips). A stocking type of anæsthesia was present in the legs. Appreciation of hot and cold was lost below the mid-thighs; pain and light touch impaired below the knees and lost below the ankle-joints. Postural sense was impaired at the ankles.

Investigations revealed a serum calcium of 6·9 mg. blood urea 59, serum sodium 315 and random blood sugars up to 450 mg.%. Other biochemical investigations, including urinary ketosteroids and nor-adrenaline were within normal limits.

The attacks were considered to be epileptic and this was supported by the EEG findings of increased theta activity in the temporal leads and paroxysmal slow activity over the frontal areas. It was observed that the attacks invariably occurred on adopting the erect position. The blood pressure under these circumstances invariably showed a rapid fall from 165/95 lying down, to 85/65 standing. Within five to ten minutes of standing, pallor, blurred vision and loss of consciousness followed and the blood pressure was too low to measure. It was not possible to prevent this postural hypotension by previously binding the patient's legs and abdomen. By the use of an antigravity suit (with the co-operation of Mr. A. M. H. Bennett, F.R.C.S.) only a slow moderate fall in blood pressure occurred without impair-

ment of consciousness. When the pressure in the suit was released the blood pressure rapidly fell and the patient lost consciousness.

Pressure on the carotid sinus did not result in significant alteration in pulse-rate or blood pressure. The Flack test resulted in a fall of blood pressure from 170/95 to 140/90. Passive elevation of the hand and forearm, on the side in which the blood pressure was measured with the patient lying down, resulted in a fall from 175/105 to 140/70. This finding suggests that defective vasomotor control is also present in the upper limbs and explains the fall in blood pressure with the "G" suit inflated.

Observations have shown that sweating was completely absent below the umbilicus and at least below the elbows. Heating the trunk and arms for one and a half hours resulted in a slow rise of temperature in the legs of 3° C. and cooling of the trunk with immersion of the hands in ice, a fall of 4° C. in the lower limbs. Scratching of the skin failed to produce a flare below the elbows or mid-thighs.

A normal increase in blood pressure was produced by adrenaline and ephedrine, though there was little change in pulse rate. Atropine (gr. 1/100 subcutaneous) also produced a rise of blood pressure without effect on pulse-rate. Although after administration of vasoconstrictor drugs the blood pressure still fell on standing, it was noted that the rise on resuming the recumbent position was considerably greater than would otherwise be produced. The subcutaneous injection of pilocarpine nitrate (gr. 1/5) produced marked sweating of the hands and arms but not below the level of the mid-thighs.

She had a grossly atonic bladder with an enormous capacity and residual urine of 7 oz.

Treatment has included regulation of the diabetes but so far the signs of polyneuritis have not changed. The blood calcium, in spite of very large doses of calciferol (250,000 units/day) remains unchanged. With the idea that increasing the blood volume might reduce the frequency of the attacks, cortisone (50 mg./day) and extra salt were tried. Possibly due to these measures there have been no further attacks during the past four months.

Blindness. ? Due to Schilder's Disease.—M. YEALLAND, M.R.C.P. (for E. A. CARMICHAEL, C.B.E., F.R.C.P.).

G. A., male aged 11 years. Admitted to the National Hospital, Queen Square, on August 20, 1955.

History.—An only child of healthy parents, he was born by cæsarean section. His early development was normal and he had had no serious illnesses.

From the age of 6 months, he had had attacks of headache, vomiting and drowsiness recurring every two or three months and lasting a few hours. For three months before admission, his vision had been failing. On the day of admission, he had become unconscious in an otherwise typical attack.

On examination.—He was drowsy and had neck rigidity. He could not perceive light with either eye though his pupils reacted to light. Both plantar responses were extensor.

Investigations.—X-rays of skull, chest and hands negative. Full blood count, E.S.R. and serum proteins normal. Blood W.R. negative. C.S.F. examination on admission—pressure 250 mm., protein 210 mg.%, no cells, Lange normal and W.R. negative. (Two subsequent C.S.F. examinations showed similar results.)

Ventriculogram normal. Fluid from the right ventricle contained protein 260 mg.% and from the left 240 mg.%.

Air encephalogram normal. Vertebral arteriogram normal.

E.E.G.s showed a gross generalized abnormality. The predominant activity consisted of high voltage irregular waves from 1–3 c/s with a fair amount of theta activity. The slow waves were predominantly occipital and arose from numerous inconstant foci in both hemispheres. No alpha rhythm could be recognized.

No definite diagnosis was made (*see* Biopsy).

BIOPSY FROM RIGHT OCCIPITAL CORTEX [3.5.56]

Dr. W. BLACKWOOD, F.R.C.S., reports: "The whole matter contains only a loose network of myelinated nerve fibres, with many swollen astrocytes and astrocytic fibres. Around the

blood vessels there are phagocytes containing both sudanophilic material and some slender anisotropic crystals. The deepest layers of the cortex show loss of nerve cells and reactionary astrocytic gliosis though most of the cortex appears healthy. The leptomeninges and subarachnoid vessels are normal. This appears to be a subacute or chronic process, the exact cause and nature of which is not revealed by the specimen. It does not have the anatomical delimitation of Schilder's disease. A vascular ætiology cannot be excluded."

[*February* 2, 1956]

Premorbid Literacy, and the Pattern of Subsequent Aphasia [*Résumé*]

By MACDONALD CRITCHLEY, M.D.

CLINICAL experience does not support the belief that aphasia is rare in illiterate persons. At the same time we do not know whether the picture of the aphasia in such individuals is unusual in its manifestations or prognosis. The situation may in other words resemble that of aphasia in a child. The problem is not a simple one; degrees of illiteracy occur and brain disease in an illiterate may often be accompanied by mutism or delirium which renders examination of the speech mechanism very difficult. The speech mechanism of poorly educated persons consisting as it does of numerous recurring modifiers, clichés, and other forms of inferior speech, stands up comparatively well to aphasia-producing lesions. In the case of brain injury to animals, it can be said that it is very difficult to obliterate animal "language" by experimental methods.

At the other end of the scale lie patients whose premorbid linguistic ability has been of a very high order. Although it is impossible to produce actual proof, it can be submitted that a highly evolved, very efficient faculty of language, spoken or written, may be expected to prove relatively sensitive to the effects of acquired cerebral disease. In other words aphasia when it occurs in an orator, wit, poet or scholarly writer, may prove to be far more severe and more protracted than in a person of mediocre attainments in the realm of language.

The question of the pattern of aphasia as occurring in a bilingual or polyglot subject is much more complicated than is suggested by the work of Ribot and of Pitres. Exceptions to the "laws" laid down by these writers are very common indeed, and it is actually unusual for an aphasiac to revert to his long-neglected mother-tongue. Many factors complicate the picture, including (1) Questions of habitual usage. Here Pitres differed from Ribot by emphasizing that the more familiar tongue might be spared rather than the original language. (2) The nature of the different languages in which a polyglot is skilled may influence the final aphasic picture. Sometimes, for example, a "dead" language is better retained than a living language, especially if it entails visual symbols of an unusual and significant kind. (3) The polyglot may speak better in the language employed by his entourage, irrespective of whether it was his earliest or even his most familiar tongue. (4) In the case of bilingual subjects the two languages might ordinarily have been employed quite differently, e.g. in speaking to servants as opposed to social and business acquaintances. This difference may be a factor in determining the pattern of the aphasia. (5) The aphasic polyglot may choose to speak in a particular language according to the topic under discussion. (6) Most important of all is the existence of a particularly strong emotional attachment which a polyglot might possess towards one language in his repertoire. This is rather borne out by the language behaviour of polyglots in other circumstances, e.g. in psychoses, in hysteria, in various organic but non-aphasic brain lesions, in dream-states and under psycho-analysis. According to Krapf a polyglot tends to use a language which in any given situation is least likely to cause anxiety and is most suited to give him a feeling of security.

The "rules" of polyglot aphasia therefore need restatement. The polyglot aphasiac (like any other aphasic patient) has a language-performance which depends largely upon his environment and upon the immediate circumstances. His verbal behaviour may be quite different in his home circle from in the clinic; in the company of a congenial intimate, than when surrounded by a critical audience. His reduced command of language may therefore be characterized by inconsistencies. On the whole the polyglot will utilize whichever language fits most easily into the immediate environment, whether by dint of the personality or nationality of the interlocutor; or because of the topic under discussion; or because of

the emotional associations attached to a particular language; or because of the superior practice-effect of a given language. The circumstances determining the choice of a language are therefore far more complex than imagined by either Ribot or by Pitres; they consitute a formula rather than a single-clause rule or law.

In aphasiacs local accent is usually somewhat exaggerated. Dialect is on the whole better retained in aphasic utterance than the correct and conventional speech. The prosodic or melodic properties of a language—which so often escape all except foreigners—are often altered in states of aphasia (dysprody). What little we know of aphasia occurring in tonal languages, e.g. Chinese, suggests that the characteristic intonations or inflections are retained so long as the language is correctly articulated. In this connexion it can be said that there is a great need for a study of aphasia as occurring in language groups outside those of the Western world.

Most ordinary people can be looked upon as bilingual of a sort—even perhaps polyglots, although they may be ignorant of all foreign languages. This is because in most tongues there is a discrepancy between the vernacular, i.e. the living flexible, ever-changing spoken language, and the written form of the same language. These differences occur in English but still more in such languages as Turkish, Arabic and modern Greek. In addition many persons employ at times a third or professional language—a jargon—depending upon their occupation or avocation. In cases of aphasia the vernacular—like dialect—as a rule is best retained, while the written, literary and professional modifications of the same language will suffer more.

On the basis of the known sex differences in the acquisition and utilization of speech, it is interesting to conjecture whether the pattern of aphasia would be different in the two sexes, the size and situation of the responsible lesion being the same.

Section of Surgery

President—JOHN BRUCE, C.B.E., T.D., F.R.C.S.Ed.

[*December* 7, 1955]

Turban Tumours

By WILLIAM J. REGAN, M.D.

Department of Surgery, University of Michigan, Ann Arbor, Michigan, and St. Bartholomew's Hospital, London

(for ALAN HUNT, M.Ch.)

St. Bartholomew's Hospital, London

TURBAN tumour is the popular name given to a type of basal cell carcinoma which arises deep in the dermis from the sweat glands or the pilo-sebaceous system. This definition is a simplification of much discussion in the literature as to the true nature and classification of the neoplasm. They were first described by Ancell in 1842 and were originally thought to be of endothelial origin, but, in 1933, Ronchese concluded that they were subepidermal in origin, beginning in the epithelium of the sebaceous glands, although others at that time believed that the sweat glands were the primary site. In 1943, Warvi and Gates differentiated between tumours arising from the sweat glands and sebaceous glands, naming the first syringomata and the second epitheliomata adenoides cysticum. However, they did recognize the possibility of a common cause and suggested that a congenital abnormality of the dermis might give rise to a variety of unusual epithelial lesions. Willis, in 1953, grouped under the term subepidermal basal cell carcinoma lesions arising from either sweat glands or pilo-sebaceous epithelium.

The lesions may involve any part of the skin, but most frequently the scalp, face, neck, chest, back, and external genitalia. When the scalp is prominently involved, turban tumour aptly describes its appearance. The familial nature of the disease is well recognized; Evans (1954) reported a 33⅓% incidence of multiple involvement. This hereditary tendency of the disease is well illustrated in the following cases. They are discussed in more detail by Chalstrey (1955).

CASE HISTORIES

R. W., a 62-year-old farmer, was admitted to hospital in March 1955, complaining of multiple nodules on the head and body. At the age of 19 he first noted a swelling on his head. During the following years a few nodules appeared on his body and by the age of 22 numerous tumours had appeared on his scalp. Many local excisions were carried out but as more were excised, more appeared. Five years ago the majority of the lesions involving the back and chest were removed. In 1954, multiple large tumours were present on the scalp but despite local removal of some two dozen in August of that year, they continued to multiply and become larger. At the time of admission there was massive involvement of the scalp. Some of the tumours had broken down and discharged a foul-smelling material. They ranged in size from 0·3 to 4·0 cm. in diameter and were of a variety of shapes, some being almost flat and embedded in the surrounding skin, others lobulated and freely movable on a short, wide base, and a few pedunculated (Fig. 1). Most had a pinkish, fleshy appearance, while others were bluish in colour. The smaller nodules tended to be firm in consistency but the larger ones were soft and rubbery and gave the impression of being cystic. Similar tumours were also present to a lesser degree on the face, neck, back, upper chest scrotum and calves.

On March 18, 1955, radical mass excision of the most severely affected area of the scalp was carried out with the application of split-thickness grafts to the defects. Fig. 2 shows the scalp seven months after operation. Histological section showed subepidermal basal cell carcinoma consisting of nodular formations covered by a thin, flat, intact epidermis (Fig. 3). Connective tissue capsules lined each tumour and projected inwards, dividing the tumour into clumps of basal cells lined by hyaline membranes. Small round deposits of hyaline material were also present between the cells and in some places there were cystic spaces and pseudoglandular formations.

Since operation the patient's head has had a total of 3,150 r at 250 kV which has caused a noticeable shrinkage of the remaining lesions.

Fig. 4 shows the patient's family tree; 12 persons are affected, 7 being female. Evans found a similar sex distribution in his collected cases. The patient's son developed turban tumours at the age of 13. A number have been excised and all have the typical histological picture of subepidermal basal cell carcinoma. One daughter first noted the tumours when she was 19. Now at age 35, multiple tumours are present over the scalp, forehead, cheeks and chin. A number have been excised and microscopic study of these reveals a similar appearance to the lesions of her father. The patient's 60-year-old brother is also affected; his tumours first appeared at age 20 and recently have been enlarging. In addition he has involvement of his neck, chest and back. The patient's youngest sister

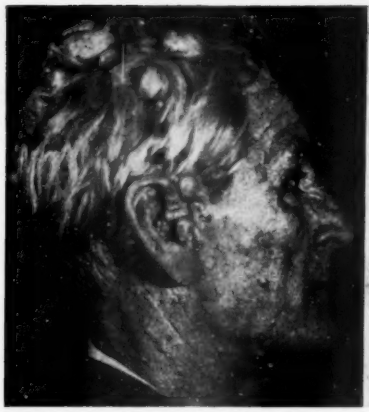

FIG. 1.—Side of patient R. W., showing the involvement of the scalp and face by turban tumour.

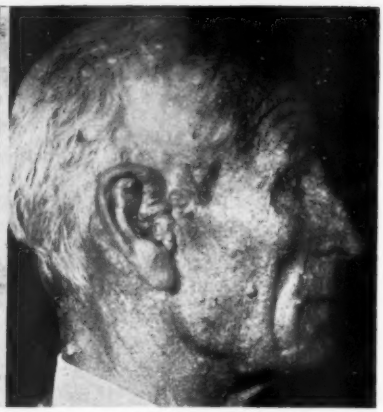

FIG. 2.—Seven months after mass excision of turban tumours and grafting. Side view; compare with Fig. 1.

FIG. 3.—Subepidermal basal cell carcinoma × 5. Note the intact epidermis, encapsulation and cystic spaces.

first became involved at age 29. Two other brothers and one sister in addition to the patient's mother, two aunts and grandmother have similar disease.

DISCUSSION

Turban tumours or subepidermal basal cell carcinoma are of rare occurrence compared to the more usual basal cell carcinoma which arises in the epidermis and is often called rodent ulcer. However, the marked disfigurement they may cause and their hereditary nature make them an interesting study. Evans (1954) surveyed the literature between 1842 and 1954 and collected 47 cases. Lyon (1955) reported another case to this Society. There was no familial history in this case. Undoubtedly there are many more cases which have not been reported or, due to disagreement as to the pathological classification, have been listed as another entity. It would seem best to discard the multitude of terms used in the past to describe these tumours and to classify them as subepidermal basal cell carcinomata of sweat or pilo-sebaceous gland origin.

SUMMARY AND CONCLUSIONS

A case of subepidermal basal cell carcinoma is described in which 11 other members of the same family have the disease. Onset is usually in adolescence or early adult life. At first the tumours enlarge and multiply slowly but by the sixth decade marked involvement of the scalp and other areas of the skin is present. The lesions do not metastasize but may occasionally erode underlying bone by pressure as in Lyon's case. They are painless and do not impair general health, but become unsightly, sometimes ulcerate, and often lead

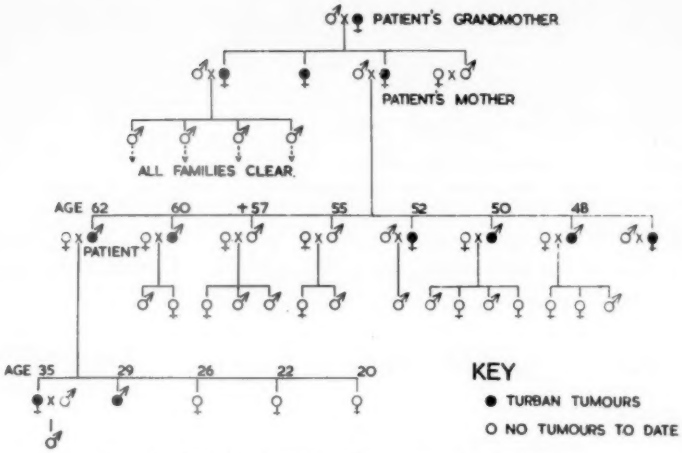

FIG. 4.—Individuals with turban tumours in one family.

to marked psychological depression of the patient. Pathological study shows them to be basal cell carcinomata beginning in the epithelium of sweat or sebaceous glands and proceeding to nodular tumours of varying size with an intact epidermis over them. Hyaline deposition with cystic and pseudoglandular formation is common and occasionally calcification occurs within them. When the disease appears, there is one chance in three that it will involve other members of the patient's family. It is an example of a Mendelian dominant trait, apparently stronger in the female sex.

The treatment of choice is surgical excision with skin grafting as necessary. X-ray therapy is of some value in that it will cause regression, but it does not cure. Evans found that those lesions treated by roentgen rays alone usually recur after a few months.

A complete descriptive term for the disease would be multiple, benign, familial, nodular, subepidermal, basal cell epithelioma, but this is far too cumbersome. When, as is usual, the scalp is the main site of involvement, the resemblance to an Eastern head-dress makes the term turban tumour a fitting title.

Acknowledgments.—Figs. 1–4 are reproduced from *St. Bartholomew's Hospital Journal* by kind permission.

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Orlon Prostheses in Arterial Surgery

By G. W. TAYLOR, M.S., F.R.C.S.,
(for Professor J. B. KINMONTH, M.S., F.R.C.S.)

BECAUSE of difficulties encountered in obtaining suitable autopsy material for stored arterial homografts and the risk of infection associated with this method, an investigation into the use of plastic arterial prostheses was undertaken.

Orlon fabric was chosen as the most suitable material. Tubes of this fabric are easily made, the seam being sewn with an ordinary sewing machine. A cuff is turned back at each end of the tube so that a double thickness of orlon is available for the anastomotic suture. The completed tubes are sterilized by boiling or autoclaving. Orlon prostheses were used, experimentally, to replace the terminal aorta in dogs, and were found to function well and remain patent over long periods. Excised specimens showed that the tube becomes surrounded by a layer of hyaline collagenous tissue which penetrates the mesh of the

fabric and which becomes lined on the lumen surface with a layer of cells indistinguishable from intima.

Orlon fabric possesses little natural elasticity and the tubes kink easily if subjected to bending strains. Orlon prostheses placed across flexion creases became thrombosed for this reason. It is considered that the best application of this material is in replacement of the terminal aorta and its immediate branches.

Orlon tubes fashioned on a bifurcation pattern were used to replace the terminal aorta in two patients with aneurysms in this situation. One patient died from renal failure after operation and the other remains well and symptom-free eighteen months post-operatively. In two further patients thrombosed common iliac arteries were replaced by orlon prostheses with good results.

A full account of this investigation was published in the *British Medical Journal*, 1955, i, 1406.

Polyvinyl Alcohol Sponge as an Arterial Substitute

By KENNETH OWEN, M.B., B.S., F.R.C.S.

St. Mary's Hospital, London

ALTHOUGH arterial homografts have demonstrated well the indications for, and limitations of, arterial replacement, they themselves have several disadvantages which have stimulated a search for artificial substitutes. The supply of homografts is limited and the methods of storage involve considerable initial expense and meticulous supervision. This paper is a preliminary communication of the early results of the use of polyvinyl alcohol sponge by the Surgical Unit at St. Mary's Hospital in comparison with plastic cloth replacements, which we have been using for the past year.

The properties required of a plastic to be used anywhere in the body have been well defined by Scales (1953), but there are additional properties required of vascular replacement material. We would list these as follows:

(1) High tensile strength in wet state.
(2) Durability: (*a*) Resistance to chemical action, e.g. hydrolysis.
(*b*) Resistance to mechanical action, e.g. work-hardening.
(3) Smooth inner lining (non-thrombogenic).
(4) Flexibility.
(5) Stretch.
(6) Not kinkable.
(7) Ease of manufacture.
(8) Ease of suturing.
(9) Porous wettable outer surface allowing fibroblast permeation, yet leakproof.
(10) Non-carcinogenic.
(11) Not producing allergy or sensitivity reactions.
(12) Ease of sterilization.

When the specification of an ideal substance was first considered it seemed unlikely that all the conditions could be satisfied in practice and some would seem to be theoretically incompatible. For example, a substance which is freely porous and wettable is more likely to undergo chemical weakening than one which is water repellent, and it is probable that some compromise might have to be accepted.

It was with these properties in mind that we started using P.V.A. sponge following work by Grindlay and Waugh (1951), and Re Mine and Grindlay (1954), who used it as a bile duct support, and Shumway *et al.* (1955) of Minneapolis who described its use for artery replacement. The material is widely used commercially for making industrial and domestic sponges. It is a long-chain polymer made by treating a foam of polyvinyl alcohol with formaldehyde. It is manufactured in this country as Prosthex (Ramer Chemical Co.) and in America as Ivalon (Clay Adams). Prosthex is slightly more dense than Ivalon and has a more uniform texture.

[A film was then shown demonstrating the making of an arterial tube. Wet strips of the sponge were wound tightly around a metal former and further compressed by bandaging. The compressed sponge was then boiled for twenty minutes and was then ready for use after removing the bandage. Various types of jigs were shown for the preparation of peripheral vessels, large arteries and aortic bifurcations.]

P.V.A. sponge has been shown by Grindlay and other workers (Hurst *et al.*, 1951) to be non-toxic, and the most interesting feature of its use in different situations is the ease with which it becomes incorporated into the neighbouring tissues. Tissue fluid rapidly seeps into

its interstices which are soon invaded by fibroblasts. There seems to be little tendency for it to become encapsulated as happens with most other foreign materials. Besides being of obvious mechanical advantage and considerably reducing the danger of infection this may also, theoretically at least, reduce the chances of late thrombosis (Egdahl *et al.*, 1955).

The first case in which we used this method was a man of 86 who had a large abdominal aneurysm which was causing him very great pain and appeared to be expanding and in danger of rupture. It was thought justifiable to use this material as he had, to say the least, a limited expectation of life and it was thought the ease of suturing the aortic prosthesis might facilitate the operation in this old man. A large aneurysm involving the aortic bifurcation was resected and replaced with a prosthesis of P.V.A. He recovered from the immediate effects of the operation but died two weeks later from a cerebral thrombosis. At post-mortem the fascinating finding was the way in which the overlying peritoneum had in many places become firmly adherent to the graft which appeared to be welded with normal tissue. The inside of the implant was covered with a smooth layer of fibrin and platelets similar to the layer which coats other types of implant.

Since then we have used this material in 11 cases with satisfactory results in all except one of the first aortic prostheses in which an inadequate amount of material was used. This was recognized at operation and the bulge was wrapped with further layers of material. An operative infection occurred—the layer became separated and rupture followed.

I should like to describe briefly two of these cases.

Case I.—Woman, aged 50, had severe radiation necrosis of all the tissues in her right iliac fossa and the right groin following X-ray treatment of a pelvic carcinoma. Her right common iliac artery had recently thrombosed. This was excised and replaced with a polyvinyl alcohol implant which functioned well.

Case II.—Man, aged 35. He presented with a mycotic aneurysm of the right femoral artery secondary to a possible staphylococcal septicæmia. The aneurysm was resected and replaced with a homograft. Three weeks later he had a secondary hæmorrhage necessitating ligation of the external iliac. He then developed a mycotic aneurysm at the site of ligation.

FIG. 1.

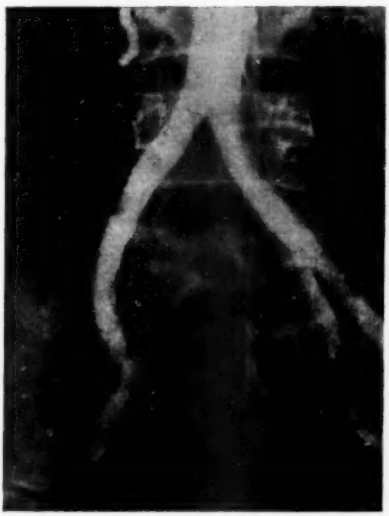

FIG. 2.

Fig. 1 is an aortogram showing the aneurysm at the iliac bifurcation. This rapidly enlarged paralysing his femoral nerve. It was resected. An attempt was made to restore continuity between the common iliac and femoral but this was impossible as his femoral was thrombosed low down in the thigh. A polyvinyl implant was therefore used to restore continuity between common and internal iliacs.

Fig. 2 is a post-operative aortogram showing a normal blood flow through the implant. Despite the presence of drug-resistant infection, the implant has survived six weeks, to date of meeting, whereas a homograft into the femoral lasted only three weeks.

We have used fabric cloth prostheses since November 1954, during which time nineteen aortic implants were performed, two being straight aortic tubes and seventeen being aortic bifurcations, but we have found P.V.A. sponge more satisfactory as it is easier to suture,

being seamless. It has a certain amount of stretch which makes it easier to overcome a disparity of lumen. It is much less liable to kink than cloth and can be made non-kinkable by reinforcing its wall at the flexion points so that it may be carried across the inguinal ligament. The smaller vessels made of sponge feel and handle astonishingly like normal artery and we feel that it is possible to obtain a much more accurate anastomosis of this material to small vessels than with a cloth prosthesis. Their resilience prevents any wrinkling at the suture line even with a fair degree of disparity of size.

The big unsolved problem of all these materials, however, is their long-term behaviour in the body. Moretz (1955) has found a 50% reduction in the tensile strength of nylon and Orlon after being buried in the abdominal wall of dogs for several months, and a less marked weakening of Vinyon and terylene (Dacron). This is presumably due to chemical changes and takes no account of the mechanical effect of the continuous strain of the diastolic pressure and the repeated deformation due to the pulse pressure. Deterling (1955*a*, *b*) has reported weakening and rupture of experimental P.V.A. grafts but these were prepared by a different method. It is interesting to note that Schofield *et al.* (1954) have reported an increase in the tensile strength of P.V.A. sponge after implantation due to the invasion of fibrous tissue. All these materials may need to be re-evaluated when these effects are fully known. We are at present conducting experiments in which we are endeavouring to speed up both the chemical changes and the mechanical strains so that we may be able to life test these materials in a few months.

Both P.V.A. sponge and fabric cloth satisfy many of the properties described earlier, e.g. not producing allergy, minimum tissue reaction, non-carcinogenic, &c., but they differ in certain points (Table I).

TABLE I

	P.V.A.	Cloth	
Tensile strength	++	+++	
Durability	?	?	
Stretch	++	—	
Non-kinkability	++	—	
Ease of suturing	+++	+	(difficult at seams)
Porous wettable outer surface	++	+	

It should be emphasized that nearly all these plastics, although given a seemingly unique chemical name, may vary in their composition and it is most important whatever material is used that uniformity of preparation should be guaranteed by the manufacturers.

We feel therefore that P.V.A. sponge is at present more satisfactory, at least in its immediate properties, but a final decision will rest upon further experience and durability experiments. If this sponge should not be ideal in this respect there are many possible ways in which it may be reinforced—for example, by a nylon net (Deterling, 1955*a*) or by bonding with cloth or fibre.

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Cinepyelography

By HOWARD G. HANLEY, M.D., F.R.C.S.

X-RAY fluoroscopy of the gastro-intestinal tract is a well-established practice and, owing to the large volume of dense contrast medium which can be used, provides reasonably good visualization once the eyes have become dark adapted. Nevertheless dark adaptation is necessary, and this prevents the use of the retinal cones with inevitable loss of clear visual definition. The light intensity can only be raised to cone vision level by greatly increasing the milliamperage screening current—which means that the patient will absorb a higher X-ray dosage, and this is obviously the limiting factor. In urological practice, the volume

and radiological density of the contrast medium is so reduced, that, up to the present, visual fluoroscopy of the urinary tract has been of very limited value.

The application of the X-ray-image amplifier to urological work has enabled us to see a clearly defined, brightly illuminated image, using a screening current of one milliampere or less (Hanley, 1955).

Film sequences were selected to show the possibilities of this principle in routine urological practice, and, in particular, to indicate the future lines of research made possible by being able to see what movements are actually occurring in a calyx or ureter under varying conditions.

Normal physiology.—Using one of the new radiologically denser media such as Hypaque, excretion pyelograms can be screened, or even cine-photographed, and the movements of the component parts of the tract viewed under physiological conditions. Retrograde pyelography gives even greater brilliance and contrast.

It is already becoming obvious that some of our previously accepted views on the emptying mechanism of the calyces will have to be revised.

While the degree of activity of calyceal contractions varies considerably from one individual to another, it can of course be influenced in any one person by changes such as diuresis, by anæsthesia and, of great significance, by posture. The classical pattern of calyceal rhythm in which each calyx is supposed to empty its contents into the pelvis in turn, prior to the emptying of the pelvis itself, has been observed in only a few instances. More often there is a haphazard pattern of contraction, with perhaps one calyx being more active than another.

Some calycine necks, though capable of sudden distension, remain "spastic" or narrow or even closed, for long periods. Others remain filled permanently, regardless of the contraction of the calyx or pelvis. Not infrequently contraction of the pelvis may cause regurgitation back into an emptying calyx rather than through the pelvi-ureteric junction. This can sometimes be seen during excretion pyelography, but is much more marked during retrograde filling, even after the catheter has been withdrawn, and one cannot help being impressed with the extreme sensitivity of the pelvis and calyces to small changes of pressure. Tilting the patient head down will result in filling of the calyces, while tilting him on to his feet will give rapid and complete emptying in a matter of seconds. In fact one is forced to the conclusion that in the absence of any obstructive element, the renal pelvis and calyces remain practically empty at all times in the erect posture. Emptying is also greatly accelerated in the prone position, and it would appear that some of our renal pathology might be avoided by sleeping on our stomachs!

Normal ureteric "*peristalsis*" is another problem under review. It is rare for one of the "columns of medium" or "spindles" to move down the ureter in a solid mass, as would occur with true peristalsis. More often the lower margin of the column empties itself into the next spindle rather like fluid running out of a burette, the lower spindle filling from below upwards.

Some pathological observations.—Several film sequences were shown depicting pathological conditions, such as ureteric calculi, ureteric strictures, hydronephroses and hydro-ureters. A hydronephrosis, even when greatly distended, may still possess calyceal and pelvic activity, and it is hoped that experience will enable us to decide before operation which cases are suitable for plastic repair or otherwise. A hydro-ureter is seldom completely inactive, and the term "atonia", even in the dilated ureters of pregnancy, is a misnomer. The contractions may be purposeless as far as fluid propulsion goes, but there is no question of atonia, while the response to stimulus by a catheter or distension can be quite dramatic.

The emptying mechanism of the bladder was illustrated by means of micturating cystograms. It is hoped that the degree of muscular infiltration in bladder carcinomas may be estimated by the degree of rigidity of the bladder wall seen during this procedure.

A short film sequence was used to demonstrate the rigidity of a calyx, in a "pre-clinical" tuberculous lesion, while the investigation of reflux in tuberculous cystitis cases is proving of great clinical value.

It is obvious that the full uses of the X-ray-image amplifier in urology are only in the process of development, but the potentialities appear to be great.

Acknowledgments.—Some of the film sequences were made for the Institute of Urology by Dr. J. J. Stevenson, while others were made at Hillingdon Hospital in conjunction with Dr. F. G. Greenwood.

I should like to acknowledge a generous grant from the Medical Research Council for the work done at Hillingdon.

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[*Continued on p. 380*]

JOINT MEETING No. 1

Section of Surgery with Section of Anæsthetics

Chairman—JOHN BRUCE, C.B.E., T.D., F.R.C.S.Ed.
(President of the Section of Surgery)

[*February* 1, 1956]

DISCUSSION ON THE APPLICATION OF HYPOTHERMIA TO SURGICAL PROCEDURES

Dr. B. G. B. Lucas (Surgical Unit, University College Hospital Medical School):

The advantage of deliberately reducing the body temperature prior to surgery is that the rate of metabolism is slowed, with a consequent fall in oxygen consumption. This fall differs from that produced by drugs inasmuch as the oxygen demand of the tissues is reduced. Under conditions of ordinary anæsthesia the oxygen consumption of the body falls because the enzyme systems are poisoned so that oxygen, although available, cannot be utilized, but with hypothermia enzyme activity and metabolism of the cell are reduced so that less oxygen is needed. Because of this lack of demand it necessarily follows that a restricted oxygen supply is less deleterious than at normal temperature. Expressed in another way, hypothermia increases the resistance to anoxia; this is of great therapeutic significance.

At present the limiting factor in many surgical procedures involving the cardiovascular system is that the blood flow cannot be interrupted for longer than a minute or two, otherwise irreversible damage to the brain and other vital organs will occur. For example, in direct heart operations the circulation has to be maintained during the endocardiac manipulations either by working on the functioning heart, or by the use of an extracorporeal heart-lung machine. The former has obvious limitations and the latter has yet to be perfected for safe use in man. In America some of the difficulties have been overcome by using human cross-circulation (Lillehei *et al.*, 1955), but there are moral objections to this and the method is outside the bounds of legality in this country. Hypothermia may be the answer to the problem because at low temperature the brain will tolerate ischæmia for several minutes, during which time operations can be carried out on the open, dry heart. Cooling also facilitates certain types of neurosurgery, such as arteriovenous aneurysms, which under ordinary conditions are extremely hazardous. Other cardiovascular abnormalities amenable to hypothermia are aneurysms of the abdominal aorta.

The increase in resistance to oxygen lack brought about by hypothermia is not the same for all tissues of the body. The brain, which at ordinary temperatures is particularly sensitive to anoxia, becomes relatively more resistant than the heart when cold. In dogs the circulation to the head can be arrested for as long as thirty minutes at 25° C. without evidence of cerebral damage, but it is not possible to stop the coronary flow to the heart for so long. This is the reverse of normal temperatures when the heart will withstand more anoxia than the brain. One explanation is that the heart does not stop immediately its blood flow is interrupted, but goes on beating for a while building up an oxygen debt, whereas the brain is virtually at rest. Alternatively, the enzyme systems responsible for metabolism of individual organs may respond differently to changes in temperature.

There are many ways of achieving hypothermia and what method is used is relatively unimportant. Surface cooling by means of ice bags or a refrigerating blanket is simple, but slow. Immersion in ice water is quicker, especially if the water is circulated around the patient so as to avoid a warm layer next to the skin. The only advantage of vascular or extracorporeal techniques is for cardiac surgery, when the chest can be opened and the diagnosis confirmed before cooling is started, and the heart can be watched throughout the hypothermic period. Whatever method is used the apparatus should be kept simple and there is no need to have large, expensive machinery in the operating theatre. For vascular cooling a satisfactory apparatus consists of a 3 lb. Kilner jar which is filled with a mixture of Dry-ice (CO_2 snow), saline and alcohol. The amount of alcohol determines the freezing point of the mixture, for example 10% has a freezing point of −4° C. The blood is circulated through a coil of 4 mm. Portex (polyvinyl chloride) tubing 16 feet in length by means of a simple roller transfusion pump (Martin, 1954), and to prevent kinking the tubing is surrounded by a wire spring. Siliconing the tubing is unnecessary (Fig. 1). For rewarming molten sodium thiosulphate (Hypo) is substituted for the Dry-ice mixture. This substance melts at 46° C. and will remain at the same temperature until it has given off all its latent heat of crystallization. The entire apparatus can be sterilized and is under the direct control of the operator (Fig. 2).

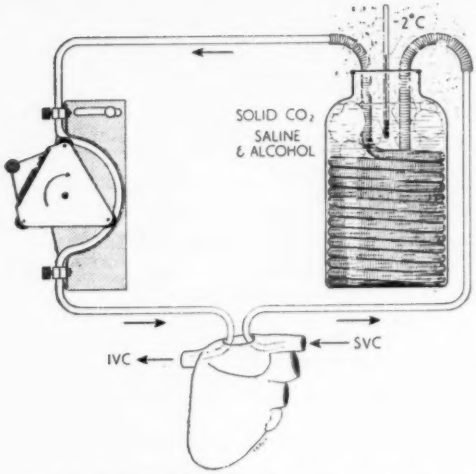

FIG. 1.—Diagram of vascular cooling apparatus.

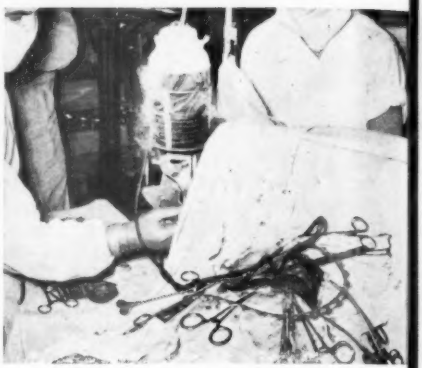

FIG. 2.—Vascular cooling apparatus in use.

The major problem is the time necessary to cool the patient. This is because of the enormous amount of heat which has to be lost. 700 large calories have to be removed to lower the temperature of a 10 st. man 10° C., which is enough to boil 1½ gal. water, or in electrical terms, the equivalent of a 1 kW fire burning for 35 minutes. This amount of heat is not removed evenly from such a large mass. Different parts of the body cool at varying rates, depending upon position, blood supply and type of tissue. For example, the rectum, being in the centre of a large mass of tissue and sometimes full of fæces, cools slowly and is an unreliable guide to the temperature of the two vital organs, the heart and the brain. That of the heart can be assessed by means of a thermometer, or a thermocouple, in the middle of the œsophagus, but there is no way of recording the temperature of the brain directly, except in neurosurgery. A thermometer in the pharynx gives an idea of the temperature of the blood returning from the brain and is usually two to three degrees above that of the heart. But the brain is a large structure and may take some time to equilibrate with the blood stream. The œsophagus is the most satisfactory place for estimating the temperature of the whole body, although allowance has to be made for the fact that with surface techniques there will be a drop of a degree or two after cooling has ceased, whereas with vascular methods there will often be an immediate rise. It is best, therefore, to wait a while in order to allow all the body to attain the same temperature (Fig. 3). What that temperature should be has not yet been decided. Since the metabolism of the body is reduced to 50% at 28° C., and to 10% at 20° C. (Bigelow *et al.*, 1950), the nearer to 20° C. that can be achieved, the better, but the lower the temperature the greater the likelihood of ventricular fibrillation. Any reduction in temperature is hypothermia by definition, but above 28° C. the benefits are doubtful and such cooling is an unjustifiable and unnecessary complication of surgical technique. At present the only indication for

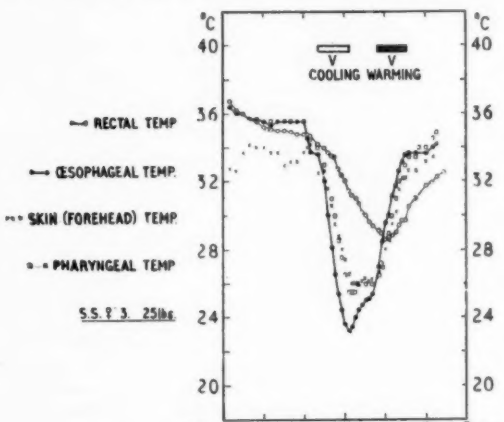

FIG. 3.—Repair of atrial septal defect: Chart showing variations in temperature during cooling.

deliberate cooling of the patient is when complete ischæmia of whole or part of the body is essential.

There are a number of practical problems in the management of hypothermia. Firstly the type of anæsthesia needed; anæsthesia is necessary to prevent shivering, which would otherwise increase heat production, but as the temperature drops the effect of anæsthetic agents is enhanced and less is required. All narcotics act by interfering with the tissue enzyme systems responsible for aerobic glycolysis so that as the need for oxygen falls with the lowering of temperature, the anæsthetic agent has a more profound effect. Therefore, short-acting agents must be used and drugs such as pethidine or chlorpromazine are best avoided. Deep anæsthesia by poisoning the brain offsets the resistance to anoxia brought about by hypothermia, so the relaxants are preferable for controlling shivering and at low temperature light nitrous oxide-oxygen anæsthesia is quite sufficient to maintain unconsciousness. This enhanced effect of drugs must also be remembered when post-operative sedation is given. The most important feature of the anæsthetic technique is deliberate over-ventilation of the patient throughout the procedure to prevent the occurrence of a respiratory acidosis. Cardiac irritability is more marked in the acidotic state at normal temperatures (Johnstone, 1950) and the incidence of ventricular fibrillation has been shown to increase if an acidosis is present at low temperature (Covino and Hegnauer, 1955). It is not always appreciated that ordinary intermittent positive pressure respiration achieved by the anæsthestist by squeezing the bag is not as efficient as it may seem. At rest the ordinary individual ventilates himself with a minute volume of approximately 5 to 6 litres, but if ventilation is performed artificially by means of positive pressure the minute volume has to be doubled if the pH of the blood is to be kept normal (Lucas and Milne, 1955). Another factor in the prevention of ventricular fibrillation is the maintenance of an adequate coronary blood flow. With a fall in temperature there is a diminution in cardiac output, but in the early stages the vasoconstriction from the direct effect of the cold is sufficient to maintain the blood pressure. At approximately 28° C. the output is so low that in spite of the vasoconstriction the blood pressure falls, with consequent reduction in coronary flow. At this stage an infusion of noradrenaline can be given with advantage (Brock and Ross, 1955). It is often impossible to estimate the blood pressure clinically in the cold patient and complicated electromanometric techniques have to be employed. In cardiac surgery a clinical impression can be formed by direct continuous palpation of the thoracic aorta.

At present hypothermia is an elaborate and time-consuming technique and can only be attempted with the assistance of a specially trained team. Temperatures and blood pressures must be recorded, the electrocardiogram observed, the blood pH estimated, as well as the actual mechanics of cooling the patient. The surgeon has the overall responsibility, so one might argue that he should be the director, but this means that he not only has to be skilled in his own craft, but also has to be a competent anæsthetist, cardiologist, and to some extent, biochemist. For the same reasons the responsibility cannot rest with the anæsthetist or cardiologist. One possible solution is for the person most experienced in hypothermia to be in charge, but to have a deputy of his own specialty so that he does not have to attend to technical details, but can be responsible for the collection and collation of all the facts concerning the patient. Moreover, all members of the hypothermic team must be completely conversant with all that is going on and not merely their own specialized job.

The future of hypothermia may well be in neurosurgery. In other branches an efficient heart-lung machine may one day be able to maintain the circulation artificially, but certain operations on the brain are technically impossible unless the blood supply can be arrested with safety. The fifteen or twenty minutes of circulatory occlusion which is possible at present is not long enough and lower temperatures will have to be reached so that the ischæmic time can be increased. Small animals have been cooled to 0° C. with survival (Andjus and Smith, 1955) and there is no reason why this cannot ultimately be achieved in man.

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Sir Russell Brock: *Hypothermia and Open Cardiotomy*

I wish to make it clear that my interest in hypothermia has been solely in obtaining temporary arrest of the circulation; chiefly in order to perform direct definitive procedures within the open heart. I have no experience of those methods in which hypothermia is used as an adjunct to anæsthesia in operations which can also be done at a normal temperature.

Similarly, in this brief communication, it is not possible to present any of the physiological and experimental details on which our work is based. I can give only a short account of our practical experiences in humans. The only physiological matter that I need mention is that our application of hypothermia depends on the lowered oxygen requirement of the body tissues at lower temperatures; the most important in this connexion is, of course, the brain. At normal temperature it suffers permanent damage if it is deprived of oxygen for 3 minutes. When the body temperature has been lowered to 28° C. it is possible to arrest the circulation for ten to twelve minutes without causing damage. At a higher temperature, e.g. 30° C., the time permitted is shorter.

Method of Inducing Hypothermia

The most popular method has been surface cooling, either by some form of cooling "blanket" or by total immersion in cold water. There are several objections to this. It may take a long time in adults; by provoking shivering it increases oxygen consumption during a time when the circulation is becoming embarrassed; it sets up other undesirable cutaneo-central reflexes; it may be difficult to control the temperature level because the fall in temperature continues after surface cooling has been stopped; circumstances are unfavourable for the rapid recognition and treatment of cardiac distress, arrest, or ventricular fibrillation; it is difficult or impossible to use it after an operation has been begun; the period of hypothermia may be undesirably long.

Although I recognize the excellent clinical results obtained by several surgeons, notably Swan, using the total immersion method, I cannot bring myself to believe that such a procedure can have a permanent place in surgery. It is both æsthetically and surgically unattractive to see a large bath of water and ice brought alongside the patient who, with intravenous drips, intra-arterial needle, ECG leads and anæsthetizing apparatus attached, is immersed. After completion of the operation, and now with a wound and a drainage tube in each pleural cavity, he is again immersed, this time in warm water.

As an alternative to surface cooling, we have blood-stream cooling.

Blood-stream Cooling

Arteriovenous cooling.—We owe to Delorme of Edinburgh (1952) and Boerema *et al.* of Amsterdam (1951) the suggestion of blood-stream cooling and after visiting the Wilkie Experimental Laboratory at the kind invitation of Professor Sir James Learmonth, in whose department this important basic work was being done, we followed the Delorme procedure, first in the experimental laboratory and then on humans. Delorme's method consists of arteriovenous cooling; a cannula is inserted into the femoral artery and blood flows through a coil immersed in ice-cold water and returns via a cannula into the femoral vein. We have found three drawbacks to this method: (i) An arteriovenous fistula is caused and this throws an extra strain on a heart that may already be weakened and may already be bearing the burden of one such fistula. As the temperature drops the heart's action and efficiency become further impaired and yet it is called upon to supply the energy to maintain the extracorporeal circuit. (ii) In spite of careful repair the femoral artery may thrombose after the operation, especially in children. (iii) The method must be started before the operation is begun; it cannot be initiated afterwards.

Venovenous cooling.—We have abandoned arteriovenous cooling for venovenous cooling and in this, as we now use it, we feel we have a method which avoids these and other disadvantages. My research assistant and now senior registrar, Mr. D. N. Ross, first suggested the principle (Ross, 1954); the method as used to-day has evolved considerably towards greater simplicity and efficiency as a result of experience both in the research laboratory and in the operating theatre (Brock and Ross, 1955). For instance, originally we cannulated the saphenous vein and the external jugular vein. Then, owing to difficulty with the neck veins in young children, we changed to insertion into the superior vena cava via the right atrial appendage. We were still left with the necessity of cannulating the saphenous vein before operation. We soon arrived at the obvious solution: cannulation of both venæ cavæ via the right atrial appendage. In this way the operation is begun at normal temperature and full cardiac exploration can be carried out, the diagnosis confirmed or completed and a final decision made as to the need for hypothermia.

Cannulæ are then inserted and the blood is circulated through a cooling coil by means of a simple hand pump (Fig. 1). The tubing is siliconized and there is no trouble with clotting. The method has the very great advantage that it can be instituted at short notice should the need for hypothermia become apparent during the course of an operation in which its use had not been anticipated. Cooling proceeds steadily and without shivering and its rate can be varied by the speed of pumping. We like to arrange a fall of about 1° C. each five minutes so that the temperature, even in a large adult, can be reduced to 28° or less in some 40–60 minutes. There is no further drop in temperature when cooling is stopped. There is

no extra strain on the heart as the venous stream is circulated by the pump. Another great advantage is that warming can be begun at once by changing the fluid in which the coil is immersed from cold to warm water. The temperature can thus be raised to 32° or 33° C. before the chest is closed. Thus the period for which the body is exposed to hypothermia is as short as possible.

While cooling is taking place the heart is under direct and constant observation so that any form of distress or arrest is at once noticed and dealt with. As an example, in a recent case in which open aortic valvotomy was to be done, ventricular fibrillation occurred at 34° C.; the heart was rapidly and successfully defibrillated; ventricular fibrillation occurred twice more, at 32° C. and at 30° C.; defibrillation was successful both times and the cooling proceeded to 28° C. and the open valvotomy safely completed. If surface cooling had been used it would have been necessary to perform an emergency thoracotomy at 34° C. and further cooling would then have been difficult or impossible.

In only one of our 39 cases have we used surface cooling and this was a small child in whom we had trouble with peripheral veins before our present technique was evolved. In 5 cases we used arteriovenous cooling; in 33 venovenous cooling; in 25 of these by our present technique of inserting both caval catheters directly via the right auricle.

So much for the method; I now come to what we have learned from using it.

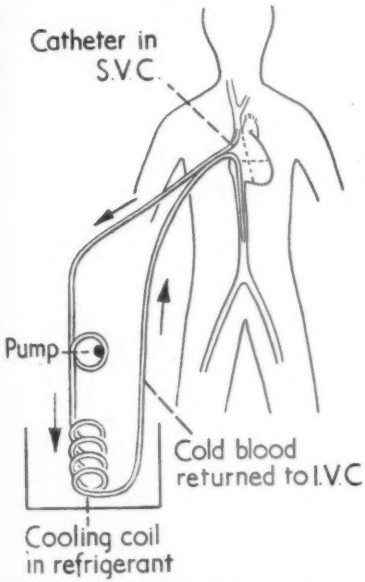

FIG. 1.—Diagram to show present technique of venovenous cooling. Blood is collected by a catheter in the superior vena cava, is pumped by a simple hand pump through a cooling coil, and is returned via a catheter in the inferior vena cava. The same apparatus is used for rewarming.

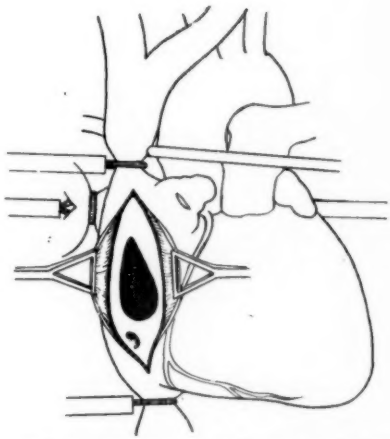

FIG. 2.—Diagram to show the circulation arrested by snaring the great vessels; the right atrium has been opened widely to expose an atrial septal defect which can then be easily closed by suture under direct vision.

PRACTICAL APPLICATION OF HYPOTHERMIA

We have used hypothermia solely for operations upon the heart or great vessels and I propose to consider our experiences under three headings: (1) Operations on the Atria; (2) Operations on the Ventricles; (3) Operations on the Great Vessels.

(1) *Operations on the atria.*—We have performed 18 open operations on the right atrium with complete arrest of the circulation; 16 of these were for closure of a septal defect; one was for removal of a myxoma of the *left* atrium; one for tricuspid stenosis and regurgitation.

Closure of an atrial septal defect (of ostium secundum type) is by far the most straightforward and successful application of the method. In any but an advanced bad risk case it enables the defect to be closed swiftly, simply and securely by direct suture and with but little risk. You may know that various indirect methods have been devised and are being used to close these defects; they include the passage of an encircling ligature round a groove

developed between the two atria, suture of the outer wall of the atrium to the edges of the defect (atrioseptopexy) and attempts at sewing the margins of the defect by sutures passed through the intact wall of the heart and guided by a finger placed in the atrial appendage. Gross uses a semi-open method in which a large rubber dam is sewn into the atrium and suturing is done by touch below the surface of the blood. This is not the time and place to debate the relative merits of these procedures; I merely put forward the policy that directs our practice. We feel that the whole future evolution of cardiac surgery is towards open definitive procedures bringing it in line with the rest of surgery; operations are to be done precisely and meticulously under direct vision. Unless and until this is proved impossible, more dangerous, or less satisfactory, we believe that our efforts should be directed to evolving and establishing open procedures in preference to closed ones.

The heart is exposed by a long transverse incision through the beds of the fourth ribs and dividing the sternum; this is virtually the standard exposure for open heart surgery. The diagnosis is verified by digital exploration of the right atrium, the finger also examining the tricuspid and mitral valves and seeking for anomalous pulmonary veins. If all is well catheters are introduced and venovenous cooling is begun; while this continues the venæ cavæ and the right common pulmonary vein are prepared for snaring. The temperature is lowered to 28° C. and the circulation is arrested by tightening the snares round the great veins and by clamping the aorta and pulmonary artery (Fig. 2). The right atrium is widely opened, the defect is inspected and then closed easily and rapidly by a continuous suture; usually 6–8 minutes is all that is needed to complete the work. The whole procedure is well tolerated even by an ill patient. We have had only one death during the procedure and that was in a woman aged 47 with chronic heart failure and severe established pulmonary hypertension. Two other patients died as a direct result of the operation; one a woman aged 49 in chronic heart failure and with systemic hypertension; the operation was uneventful and her condition was satisfactory until she died quite suddenly a few hours later, presumably from acute right ventricular failure. The other was a boy aged 17 who, in addition to an atrial septal defect, had total anomalous venous drainage of the right lung which could not be corrected; he died twenty-four hours later.

The first two patients should never have been operated on; it is almost useless expecting to save these middle-aged patients whose myocardium has begun to fail after nearly half a century of overwork and strain. I do appeal to physicians and cardiologists not to make it even more difficult for their surgical colleagues to establish new and anxious fields of surgery by asking them to operate on these advanced, hopelessly bad risk cases. It saps morale, delays progress and destroys confidence between physician and surgeon. I urge my surgical colleagues not to accept such cases and so discourage this policy of serving up bad material and expecting miracles to be achieved with it.

I have no hesitation in saying that except in these hopeless cases in severe failure, the open closure of an atrial septal defect under hypothermia is a safe, sound and successful surgical procedure which can be recommended with complete confidence.

I have said that our practice of open operation on these defects rests on our policy of striving to develop open heart surgery and this experience in operating on the open right atrium has already begun to justify itself and to pay dividends.

Thus it has enabled us to operate on the tricuspid valve under direct vision. I have found the relief of tricuspid valve stenosis is not satisfactory by the finger technique as used with such success in mitral stenosis. It is difficult to be certain just where the commissures lie and, moreover, the stenosis is commonly accompanied by a considerable degree of regurgitation. I have recently operated on a patient on whom at a first operation I performed combined aortic and mitral valvotomy; she was left with disability due to severe tricuspid valve disease, partly stenosis, chiefly regurgitation. With venovenous cooling the temperature was lowered to 25° C. which gave ample coverage for the 7¼ minutes during which the circulation was arrested and in which the stenosis was relieved and a plastic repair done on the valve. The heart was quite undisturbed.

Yet again, our experience with the open right atrium suggested what I am confident is the correct route for removal of myxoma of the left atrium. This peculiar tumour simulates mitral stenosis and until recently had never been diagnosed during life. With thousands of operations being performed on mitral stenosis it is inevitable that more cases should appear and that some should be discovered during life. Attempts at removal have usually not been successful although Crafoord (1954) has had one success. In addition to the problem of diagnosis there is the problem of removal which introduces all the difficulties of opening the left side of the heart, of air embolism and of the fragility of the tumour itself. Recently my assistant, Mr. Ross, operated on what was thought to be a typical severe case of mitral stenosis and found a large polyp filling the left atrium; the mitral valve was normal. He was obliged to retreat. Unfortunately palpation of the tumour had caused cerebral embolism and a hemiparesis. The patient's condition was grave when I saw her on the following day. Rightly

or wrongly I decided that the correct course was early removal of the tumour as it seemed very unlikely she would survive to have it done some weeks or months later and we have learned to our cost that delay means great difficulties from pericardial exudate, soft myocardium and other problems. Also she was in danger of further embolism.

Operation was done under hypothermia on the third day after the exploratory operation; the heart was approached through the right chest which had the advantage of avoiding the previous operative field and the incised sutured, thrombosed left atrium. I had realized from experience with *closure* of a septal defect, that it was just as easy to approach the left atrium by *opening* the atrial septum; the obliquity of the septum also favours the approach from the right side. The septum was exposed after opening the right atrium, was incised, and it was a matter of little more than moments to insert a dessert spoon and to remove in one movement the tumour and the large mass of associated clot; the interior of the left atrium was then freely inspected before closure of the septum. Unfortunately ventricular fibrillation occurred and satisfactory heart action could not be restored; not surprising when one considers her grave state. Perhaps we should have been successful if we had waited some months; I am confident, however, that if the tumour had been diagnosed before operation and the right atrial approach had been used as a preliminary procedure, success would have followed. This is clearly the route to use in other such cases.

(2) *Operations on the ventricles.*—I cannot speak with such assurance about operating on the ventricles under hypothermia as I can about the atria. At the same time I do not support the statements made that hypothermia is unsuitable for operations on the ventricles; these conclusions have been made on insufficient evidence and experience. Our own experience in 12 cases of open ventricular cardiotomy has told us something of the advantages and disadvantages. Time does not permit a full presentation, but it appears that there has been confusion between the effects of pure ventricular cardiotomy and the effects of operating in the presence of certain advanced cardiac pathological states such as severe pulmonary hypertension.

Thus in 6 cases I have used ventricular cardiotomy to effect a simple resection of a stenosis; in 3 open resection of a pure infundibular stenosis with closed septa; in 3 open infundibular resection and valvotomy in Fallot's tetralogy. 5 of these were successful; one child aged 11 months with Fallot's tetralogy succumbed. Ventricular fibrillation occurred in all, but normal rhythm was restored without difficulty. The usual objection made to ventricular cardiotomy under hypothermia is the incidence of ventricular fibrillation; this is not a real problem.

Pure infundibular stenosis is a condition demanding open visual resection; not only does this allow complete relief of the stenosis but permits avoidance of the tricuspid valve mechanism which is closely attached to the stenosis and can scarcely be avoided in a closed operation, as I know to my cost, having caused severe tricuspid regurgitation in this way. Hypothermia provides a simple and effective means of arresting the circulation for the 5–10 minutes needed for this procedure; it is, at present at any rate, less dangerous than the various other methods of securing a dry field for ventricular cardiotomy, especially the various heart-lung machines.

Relief of the stenosis in Fallot's tetralogy is also no problem; however, if this is done the ventricular septal defect remains and if the stenosis has been freely removed, flooding of the pulmonary circulation follows. I have attempted simultaneous closure of the ventricular septal defect in 4 cases but without success. In one case death occurred from cerebral anoxia due to a technical fault in cooling; the surgery seemed successful.

I have also attempted closure of an isolated ventricular septal defect by open suture in 2 patients without success; both were severely ill.

I am convinced that in this latter group, hypothermia is unsuitable. Most of the patients are infants or young children with severe secondary pulmonary hypertension and episodes of congestive failure. The left-to-right shunt is large and the systemic circulation starved and feeble; the child seems unable to stand the necessary cardiac manipulations, especially the introduction of the caval catheters which have the effect of reducing still further the poor systemic venous return. Lillehei has commented on this and has demonstrated that the only hope of success in these cases lies in being able to assist the circulation powerfully and promptly. This he has achieved by cross-circulation and by his pump-oxygenator.

Although hitherto unsuccessful I do not feel that the problem of treatment of Fallot's tetralogy under hypothermia is so unfavourable. I hope that we can overcome the technical problems which have defeated us so far. I feel some confidence that the basic physiological state in Fallot's tetralogy is much more favourable because of the good systemic circulation; our caution should be directed towards overtaxing an anatomically poor pulmonary circulation. We may yet demonstrate that a total operation can be safely carried out under hypothermia even though the intracardiac operating time permitted is rather short.

(3) *Operations on the great vessels.*—Here again I must mention some applications of

hypothermia which we have found unsuitable, namely for secondary operations on recanalization of persistent ductus and secondary aneurysm formation associated therewith. These are dangerous and anxious cases in which the surgeon is faced with the prospect of sudden massive uncontrollable hæmorrhage. For this reason I used hypothermia on 3 such cases; all died. We found that the heart, struggling under the large arteriovenous shunt, is very liable to develop ventricular fibrillation and, in the continuing presence of the severe shunt, resuscitation is not possible. I consider this is a wrong application of hypothermia and now prefer hypotonia as an aid instead.

Another condition in which the surgeon fears severe hæmorrhage is aorto-pulmonary septal defect; this may be diagnosed before operation or may be found during exploration of what was thought to be a straightforward persistent ductus. In such cases hypothermia can and should be used; we have used it in 2; in one with complete success; the other patient died owing to a surgical technical failure and not to hypothermia.

I come now to the use of hypothermia to enable stenosis of the pulmonary valve or of the aortic valve to be corrected under direct vision by opening the pulmonary artery or the aorta.

Varco (1951) was the first to perform open transarterial pulmonary valvotomy, but it was Swan and Zeavin (1954) who developed the method under hypothermia. I shall not debate the merits and demerits of this procedure; I would merely point out that it can be done simply and safely under hypothermia and since little more than 4–5 minutes is required the temperature need not fall below 30° C. We have performed open pulmonary valvotomy on three occasions under hypothermia; all have been successful.

With aortic valve stenosis we have a different problem; much more complex. In most cases the valve is so calcified that it is difficult or impossible to restore valve function by blind closed methods; all we can hope to do is to lessen the stenosis. Even under direct vision little more could be achieved in these calcified cases; the valve is too bad. Moreover, in most of these cases the myocardium of the left ventricle has been under such long-continued strain that it is unlikely to tolerate hypothermia well. The great hope in aortic stenosis lies in being able to operate before the valve has become heavily fibrosed and calcified; this means operating on children or young adults. Although not common, enough cases are seen in children to indicate that in these we have a surgical problem worthy of satisfactory solution. I have performed closed aortic valvotomy on a number of children with some good, some fair and some poor results. The greatest problem is to relieve the stenosis satisfactorily and not cause severe regurgitation. This latter has been responsible for late death in two of my cases and was found by Marquis and Logan (1955) to constitute the greatest drawback to operation. Indeed they concluded that they were probably in error in having operated on the children. It is clearly not satisfactory to have to reject a sound surgical step such as the relief of a fibrous obstruction because of technical limitations. The problem would clearly be much easier if the valve stenosis could be divided under direct vision for in this way the best possible result could be obtained. We have shown that open aortic valvotomy is indeed possible under hypothermia. The procedure was well tolerated in a boy of 11; the circulation was arrested for 7¼ minutes and although ventricular fibrillation occurred after 5 minutes no difficulty was experienced in restoration of normal rhythm. Four patients have now undergone open aortic valvotomy.

I think I have said enough about our experiences to convince you that with hypothermia we have a valuable means of performing definitive surgery on the open heart, a very important and desirable technical state. I would especially emphasize that it has enabled us to operate under direct vision upon 3 of the 4 heart valves.

All this has been achieved by two things, in addition of course to the fundamental contributions made by several men throughout the world. The first is by team work; a large team of keen and willing helpers is essential for success in such a difficult field and I have been very fortunate in having such a team to work with. The second is that this type of surgery cannot be done without collateral experimental laboratory work; for this one must have an organization and such an organization needs financing. I would like to pay a tribute to the generosity and wisdom of the Governors of Guy's Hospital who have set aside large sums of money from the Endowment Fund over several years for this research.

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Dr. T. Cecil Gray (President of the Section of Anæsthetics) said that he was particularly interested by Sir Russell Brock's method of arteriovenous cooling for thoracic surgery and was completely convinced that this was a preferable method for this type of work. However, he felt a little unhappy in regard to Sir Russell's wholesale condemnation of surface cooling —a method which, on his own confession, he had not tried. Clearly Sir Russell's method of cooling was not suitable for neurosurgery, nor for cooling during general surgical procedures or for therapeutic hypothermia.

Sir Russell Brock's condemnation of surface cooling as, "æsthetically repellent," could not be taken seriously; neither could the suggestion that this method was "shivering promoting". For with his colleagues he had dealt with just on 200 cases for surface cooling and in the last 150 there had not been one case of shivering. Sir Russell had also mentioned the afterdrop of temperature as a drawback with this technique. The temperature did fall after cooling was stopped in certain types of individuals, but he thought one could tell the sort of individual in which this would occur and allowances could be made for the fall of temperature which would follow the termination of the cooling process. There was not, as had been suggested, any difficulty in maintaining the hypothermia once it had been attained. These patients remained at the required temperature until the rewarming process was commenced.

Although Dr. Lucas had condemned hypothermia for any procedure other than neuro- or thoracic surgery, one should remember that it had been found very useful in certain conditions such as acute thyroid crises, hyperthermia and various neurological disturbances. Furthermore, there was a little evidence that in certain cases where surgery must be carried out on extremely poor risks, and very elderly patients, hypothermia was beneficial.

Professor Charles Rob said that there was only one proven indication to-day for hypothermia, namely, when the blood supply to some portion of the central nervous system was to be cut off, and this included stopping the heart during intracardiac surgery. Another and less clear indication was in those surgical operations which include clamping of the blood vessels to the kidney or liver. He agreed with Dr. Lucas that there was not much place for hypothermia in general surgery, at least until the subject was more completely understood.

Three years ago he was operating under hypothermia on a patient with an aneurysm of the upper abdominal aorta. The patient was given an intravenous solution of glucose during the procedure and at the same time the plasma electrolytes were estimated at regular intervals. These fell to a very low level, the reason being that under hypothermia the glucose was not metabolized; the blood sugar rose and this resulted in a fall of the plasma electrolytes by dilution.

Dr. H. L. Rosomoff (U.S.A.) said that he was very pleased to find so many people in England sharing the opinion that hypothermia had a great potential use in neurological surgery. This was an inevitable conclusion when some of the effects of hypothermia on the normal and abnormal physiology of the nervous system were considered.

During hypothermia, there was a decrease in cerebral blood flow, at a rate of 6·7%/° C. There was a corresponding reduction in cerebral metabolism so that at 25° C., both metabolism and blood flow were one-third of the pre-cooling level. A decrease in mean blood pressure was often found which might be maintained for long periods of time without the appearance of any untoward effect, and thus it might be considered to be an induced, "compensated" hypotension. There was a reduction in brain volume of 4·1% at 25° C. which, in man, would amount to a change of 55 ml., a considerable volume when dealing with problems coincident to the expansion of the intracranial contents. There was also a decrease of cerebrospinal fluid pressure, at a rate of 5·5%/° C.

These effects might be used to great advantage when hypothermia was employed as an adjunct to neurological surgery, particularly in the treatment of cerebrovascular anomalies. Blood flow was decreased which facilitated hæmostasis; the brain was "slack" and intracranial pressure reduced which enhanced surgical exposure. This made surgery easier technically, more expeditious, and resulted in a minimum of trauma and blood loss. In addition, there was a safety factor against the consequences of extended temporary or permanent interruption of major vascular channels. In the latter instance, he had been able to demonstrate that when *permanent* interruption of the middle cerebral artery of the dog occurred during hypothermia of 22–24° C., cerebral infarction was minimized or prevented. If this finding could be transposed to man, then many vascular lesions in and about the circle of Willis which now were considered inoperable might become amenable to correction, thus offering definitive and curative treatment to patients to whom such surgery had hitherto been denied.

Dr. B. A. Cookson, said that ventricular fibrillation could occur in the hypothermic state even when the chest had not been opened and the heart was healthy. However, it was true that when the chest was open and the ventricles were handled the incidence of ventricular

fibrillation was much higher. The heart was particularly sensitive in this respect during the summer—at least in the U.S.A. where the summer temperature was 80–90° F. (27–32° C.).

He stressed the importance of the laboratory in the development of hypothermia. Not only had hypothermia come from the laboratory, but the laboratory had served as an invaluable training ground for surgeons who wished to use this method clinically. It was unfortunate that some surgeons who employed hypothermia clinically had not had laboratory experience. In this country the fault partly lay in the fact that the facilities for experimental animal surgery were not adequate.

Mr. I. K. R. McMillan said that while in the United States he and Drs. R. Case and W. Stainsby had done work on the function of the hypothermic ventricle. They, like previous observers, had found that the coronary flow in hypothermia diminished rapidly; for example, coronary flow in a 60 lb. dog was on average 60 c.c./min. If the temperature was reduced to 22° C. it would require only 6 c.c. per minute but at the same time the mean aortic pressure would only fall 33% (from 90 mm. to 60 mm.Hg). It was therefore unlikely that there was a deleterious effect from the reduction in coronary flow. If the minute work of the left ventricle was plotted under hypothermic conditions it was found that the heart was doing more work for less coronary flow at these temperatures than in normal temperatures, and further that if the heart was put under strain by transfusion to raise the filling pressure and the amount of work it was doing per stroke was estimated, it appeared to behave as well or better in many instances at 28° C. than it did at 37° C.

They had made an observation in arteriovenous cooling that if the temperature was measured in the aorta during cooling and the cooling coil was shut off when the reading was 28° C. there was a rebound of 4° C., and it took about half an hour to level off before the temperature was steady. To reach 28° C. the animal therefore had to be cooled down to about 3° C. below this, to get a final blood temperature of 23° C. This might be a possible explanation of the spontaneous ventricular fibrillation that sometimes occurred during the cooling process, as the circulating blood was therefore colder than the rest of the tissues.

The Chairman said that general surgeons were a little concerned about the application of this method to general surgery which could be carried out satisfactorily under other anæsthetic techniques. He was very struck by the paper from Johannesburg (Knocker, 1955, *Lancet*, ii, 837) showing the disastrous changes in the vital organs in hypothermia. He wondered if anyone present had had any experience of the post-mortem pathology in patients dying after hypothermic procedures or whether there was any one present who could say anything about that side of it.

Dr. Rosomoff (U.S.A.) said that to date, there had been no mortalities among his patients subjected to hypothermia for neurosurgical procedures, so he could not comment on this question from clinical experience with man. However, his group had made extensive gross and microscopic studies of the vital organs of experimental animals in which hypothermia had been used as an adjunct to neurological, cardiovascular, and hepatic surgery. They had failed to demonstrate any significant abnormalities attributable to the effect of hypothermia at post-mortem examination, nor had there been any untoward effects on objective clinical examination. Of course, these were experiments in which the animals had been rewarmed to normothermic levels and then observed for variable periods of time post-operatively. From Dr. P. Knocker's protocol there was reason to suspect that her animals might have been hypoxic and/or acidotic, not as a consequence of hypothermia *per se*, but as a result of inadequate ventilative technique. The fact remained that the alleged changes had not been found in experiments where the animals had been rewarmed and then examined. Therefore, before Dr. Knocker's thesis could be accepted, confirmation or negation of her results must be obtained from other sources; and if she were proved correct, an explanation must be found for the apparent disparity between her findings and those of survival experiments.

Dr. B. Fisher (U.S.A.) demonstrated a slide which showed some recent work done in prolonged hypothermia in studies on the liver. The metabolism of the liver was studied from many aspects, biliary secretion, composition of the liver, oxygen consumption and so on. It was shown that after one hour of ether anæsthesia there was a depression of bile volume and cholic acid which returned to normal within twenty-four hours. The same thing happened with cholic acid following hypothermia up to six hours. Within eighteen hours after rewarming the bile volume and the cholic acid concentration were back to normal. Following twelve hours of hypothermia at 22° C., the bile volume and cholic acid returned to normal after a slightly longer time; in the case shown within thirty-two hours. He had found that after twelve hours of hypothermia of 22° C. in dogs there was no perceptible damage to the liver. After twelve hours one began to get metabolic changes which were irreversible, and he pointed out that surgeons should be careful as to the duration of hypothermia.

Dr. B. G. B. Lucas, in reply, pointed out that our knowledge of hypothermia was still inadequate, and pleaded for caution until more experimental work had been done, otherwise a valuable technique might fall into disrepute. Concerning liver damage, he had not seen any evidence of this either in animal experiments or in human cases.

Section of Comparative Medicine

President—Professor JAMES MCCUNN, F.R.C.S., L.R.C.P., M.R.C.V.S.

[*December* 14, 1955]

MEETING AT THE ROYAL VETERINARY COLLEGE, LONDON

NEW APPARATUS AND METHODS OF INTEREST IN ANÆSTHESIA, RESPIRATION AND RESUSCITATION

The following films were shown:

Cardiac Surgery in the Dog under Hypothermia.—Dr. B. A. COOKSON.
Cæsarean Section in the Cow.—Professor C. FORMSTON.
Anæsthesia in Wild Animals.—Mr. OLIVER G. JONES.

The following demonstrations were given:

Hypothermia Blanket for (Human) Clinical Use.—Dr. B. A. COOKSON.
The Phrenic Nerve Stimulator.—Dr. K. W. CROSS and Dr. P. W. ROBERTS.
An Artificial Heart and Lung Machine for Use in Man.—Dr. D. G. MELROSE.
A New British Cuirass Respirator and Adaptor Unit.—Dr. J. T. SCALES and Dr. A. B. KINNIER WILSON.
Electrographic Monitoring of Anæsthesia.—Dr. B. WYKE.
Infra-red Analyser for Rapidly Changing Respiratory Carbon Dioxide Concentrations.—Dr. A. BRACKEN.
(1) Apparatus for Recording Tidal Volume and Rate During Artificial Respiration in the Anæsthetized Subject. (2) Amplifier to Convert a Cossor ECG into Single Channel EEG Apparatus.—Dr. R. P. HARBORD and Mr. P. W. RAMWELL.
Intermittent Positive Pressure Respirators.—Professor E. A. PASK.
The Pneumotron: A Positive Pressure Respirator.—Dr. J. P. PAYNE.
Apparatus for Prolonged Intermittent Positive Pressure Respiration.—Dr. J. M. K. SPALDING and Dr. A. CRAMPTON SMITH.
A Sonic Gas Analyser for the Continuous Measurement of Carbon Dioxide in Expired Air.—Dr. F. STOTT.
Intermittent Positive Pressure Respirators for Thoracic Surgery.—Dr. R. W. WELCH and Dr. J. ROCHFORD.
Apparatus for Neo-natal Anæsthesia.—Dr. R. W. COPE.
Portable Apparatus for Resuscitation or Anæsthesia.—Dr. H. G. EPSTEIN.
The Aintree and Fazakerley Respirators.—Dr. J. ESPLEN.
A Blood Pressure Follower.—Dr. J. H. GREEN.
Endotracheal Methods in the Larger Farm Animals.—Mr. L. W. HALL.
Cyclopropane-oxygen Anæsthesia of Ruminants.—Mr. A. G. SINGLETON.
Trilene Inhalers.—Dr. G. C. STEEL.
Paravertebral and Lumbar Epidural Anæsthesia in the Bovine.—Mr. L. C. VAUGHAN.
A Respiratory Anemometer.—Dr. B. M. WRIGHT.
Anæsthetic Techniques in the Dog and Cat.—Miss B. M. WEAVER.

[*January* 30, 1956]

DISCUSSION ON HYPOTHERMIA

Dr. H. C. Churchill-Davidson: *Hypothermia in Perspective*

Hypothermia means a fall in the body temperature below its normal resting level. Strictly speaking, therefore, any temperature below 98·4° F. or 37° C. should be regarded as hypothermia, but the term is usually restricted to temperatures of 93·2° F., 34° C. or less.

The principal reason why the spotlight of publicity has become focused on this subject is that future progress in cardiac surgery demands that some method be evolved whereby the surgeon can operate upon the heart under direct vision instead of by the sense of touch, as at the present time. The goal, therefore, is to stop blood flowing through the heart, so that one of the chambers can be opened, any defect visualized and repaired, and then the heart closed without the concomitant ischæmia causing irreversible damage in any of the other vital organs. There are two possible lines of approach to this problem. First, the heart and lungs can be isolated from the circulation and their work temporarily taken over by a mechanical pump-oxygenator. Secondly, the oxygen requirements of each cell may be cut down by

lowering the general body temperature. The latter is the principle of hypothermia, and its possible application to cardiac surgery was first explored by Bigelow of Toronto in 1950 (Bigelow *et al.*, 1950). Since then the use of this technique has spread to many other branches of surgery, and our knowledge of the basic physiology of cold has improved.

All hibernating animals are relatively small and the largest known hibernator is the Canadian ground hog or marmot, weighing up to 5 kg. Bigelow was impressed with the fact that nearly all hibernating animals have a pad of brown fat in their axillæ and anterior mediastinum. He regards this fat as a possible hibernating gland but up to the present time he has been unable to isolate any active secretion which, after injection, is capable of inducing hibernation in another animal, even of the same species.

Animals which do not hibernate respond to cold by constriction of the skin vessels and by shivering in an attempt to make enough heat to maintain a normal body temperature. Deep anæsthesia or paralysing the muscles with a muscle relaxant, however, abolishes the shivering reflex so that the animal's body temperature tends to fall to that of its surroundings.

Each species of animal appears to have a critical temperature around which the heart stops. Generally speaking, the smaller the animal the lower is this temperature, and similarly, the younger the animal the better can it withstand low temperatures as compared with its parents. Cessation of the heart beat is usually regarded as one of the criteria of death, but Andjus and Audrey Smith (1954) have shown that this is no longer tenable for some hypothermic animals.

The main danger of hypothermia is spontaneous ventricular fibrillation. Thus, as the temperature falls so the myocardium becomes more irritable until finally a stage is reached when the normal rhythm may suddenly give way to fibrillation. If this does not occur the heart beat gets slower and slower until it finally stops altogether. Certain factors such as anoxia, a high carbon dioxide tension, and changes in the electrolyte balance, all tend to make the myocardium more irritable and therefore to require special attention. The actual temperature at which this myocardial irritability becomes evident varies from species to species. In man the difficulties that have been experienced in restoring normal rhythm after ventricular fibrillation has developed during deep hypothermia have tended to make people wary of using these low temperatures. In other words a "cold barrier" has arisen so that temperatures of 30 to 28° C. are now regarded by most anæsthetists as the optimum level in adults. This permits interruption of the circulation for about eight to fifteen minutes in adults. If much lower temperatures could be reached with safety, however, the operating time would be much longer. In very young children a temperature of 26° to 24° C. can usually be reached with safety.

Hypothermia has now been used extensively both in this country and the United States for the repair of the atrial septal defects and for operations on the great vessels. Similarly, it has found a place in the treatment of certain vascular brain tumours, but the incidence of spontaneous ventricular fibrillation has not warranted its use for general surgical procedures. This may seem to place undue emphasis on the danger of ventricular fibrillation now that we have the aid of electrical defibrillation. The future will decide this point. It would theoretically seem more physiological to follow D. G. Melrose's suggestion and deliberately stop the heart, so that its metabolism is minimal, rather than to allow the heart to fibrillate.

There are two possible methods of inducing hypothermia in an adult patient—surface cooling and blood cooling. Surface cooling is the most widely adopted method, and consists of cooling the patient's skin either by immersion in cold water or by surrounding the body with ice bags or a refrigerated blanket. The other method, introduced by Delorme of Edinburgh (1952), cools the blood directly. Originally blood was taken from an artery and cooled as it flowed through some tubing back into a vein. This method has now been modified by Ross (1954), whereby blood is taken from a venous channel, pumped through a cooling chamber, and then returned to the inferior vena cava. Much time and energy has been expended in extolling the merits and demerits of surface versus blood cooling. Surface cooling is slower but easier to perform, particularly in small children. Blood cooling is quick and has the advantage that it need not be started until the outside of the heart has been examined at operation. Against this there are those who argue that special skill is required to cannulate major vessels, which entails risks. In essence it does not seem that the method of cooling used is of great importance. Our attention should be directed towards the more vital matters of physiology, and I hope that many of these problems will be fully discussed in the subsequent papers.

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Dr. Audrey U. Smith (National Institute for Medical Research, Mill Hill):

Resuscitation of Hypothermic, Supercooled and Frozen Mammals

Natural hibernation follows a preparatory period of many days or weeks after a fall in the environmental temperature. During this period the animals find a sheltered hiding place and put on weight or lay in food stores. Furthermore, their tissues undergo fundamental biochemical changes. For instance, the body fats become desaturated so that they stay soft at lower temperatures (Fawcett and Lyman, 1954). When the animals finally hibernate they become profoundly lethargic and their deep body temperature drops from the normal level of +38° C. and may reach as low as +3° C. The deep body temperature does not, however, reach 0° C. because heat production continues at a low level (Lyman and Chatfield, 1955). The tisues of animals in hibernation do not, therefore, become frozen. Furthermore, if the temperature of the immediate environment falls below 0° C. there is an increase in metabolic rate, sufficient to prevent the body temperature from falling and in many instances so great that the animals actually rouse from hibernation (Lyman, 1948). In natural hibernation breathing and heart beats are slowed but never stop completely. The animals are not inanimate nor are they anæsthetized. Gentle handling, let alone surgical interference, will cause them to rouse. By contrast, when the same animals are experimentally cooled from normal temperatures at a time when they are not hibernating a state of anæsthesia is reached by the time the body temperature is + 8° C. Below about +3° C. respiration and circulation are arrested and the animals do not recover spontaneously in warm surroundings. They are apparently dead.

Newborn mammals of non-hibernating species tolerate hypothermia to approximately the same degree as hibernators, but for comparatively short periods (Fairfield, 1948). By the time they are adult their thermal adaptability has decreased so that they will not withstand cooling to body temperatures lower than 25° to 15° C. At some temperature in this range, depending on species, breathing ceases and, shortly after, the heart comes to a standstill so that the animals appear to be dead.

Until quite recently there seemed no hope of resuscitating either hibernating or non-hibernating animals which had been kept with arrested circulation and respiration at body temperatures above zero. The prospect of storing whole mammals in the frozen state seemed even more remote because of the damage to cells and tissues which occurs when water separates as ice and the salt concentration in body fluids increases. It must be emphasized at this point that cells and tissues of hibernating mammals do not tolerate freezing and thawing *in vitro* any better and, in some instances, their tolerance is less good than those of non-hibernators. Thus, the red blood cells of hamsters hæmolyse more readily than those of humans or rats during freezing and thawing or when exposed to hypertonic salt solutions (Lovelock, 1956). Damage due to freezing and thawing can, however, be prevented *in vitro* by incorporating glycerol into the medium in which cells and tissues are suspended, and by cooling them slowly. This proves that neither intense cold nor crystallization of water as ice is necessarily lethal to living cells (*see* Smith, 1954*a*).

In 1951, Dr. Andjus reported from Belgrade that he had succeeded in reviving 20% of adult rats in which breathing and heart beat had been at a standstill for one hour and in which body temperature had dropped to between +2° C. and 0° C. (Andjus, 1951). This was the first demonstration that mammals could survive prolonged respiratory and cardiac arrest at reduced body temperatures. During part of 1953 and 1954 Dr. Andjus worked at the National Institute for Medical Research and during this year methods were evolved which permitted revival of 75 to 100% of rats from body temperatures a little above freezing point (Andjus and Smith, 1955; Andjus and Lovelock, 1955). The animals, which had been without respiration or circulation for one hour, survived long periods thereafter. Their behaviour was not altered and psychological tests showed that memory was not significantly impaired (Andjus *et al.*, 1955). Meanwhile, Niazi and Lewis (1954) had resuscitated rats after cardiac standstill lasting 35 to 44 min. at deep body temperatures averaging +5·3° C.

Chilled golden hamsters were easier to resuscitate than rats and also survived longer periods of respiratory and circulatory arrest when kept on ice with body temperatures just above freezing point. Seven hours was the limit for storing them under these conditions. We therefore turned our attention to the effects on hamsters of exposure to sub-zero temperatures.

When isotonic saline, or blood or any other body fluid is chilled, ice may start to form as soon as the freezing point of the fluid is reached. Alternatively, supercooling may occur. In exactly the same way, some of the hamsters froze progressively and others became supercooled when immersed in baths at −5° C. to −7° C. Animals which had been freezing for periods up to 1 hour and others which had been supercooled to deep body temperatures between −5° and −6° C. recovered completely.

The techniques for resuscitating hypothermic, supercooled and frozen mammals after respiratory and cardiac arrest have been illustrated in a film and described elsewhere (Andjus and Lovelock, 1955; Smith *et al.*, 1954; Smith, 1954*b*).

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Lieutenant Hubert L. Rosomoff, M.C., U.S.N.R. (Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland):

Some Effects of Hypothermia on the Normal and Abnormal Physiology of the Nervous System[1]

The use of hypothermia as an adjunct in cardiovascular surgery is based on the principle that the decrease in body temperature produces a reduced metabolic rate, which then permits the extended exclusion of the brain and spinal cord from the general circulation. This concept originated when studies of the effect of hypothermia on total body oxygen consumption demonstrated that oxygen utilization was markedly decreased at low body temperatures (Penrod, 1949; Bigelow *et al.*, 1950). It was then, and has since, been assumed that total body oxygen consumption and cerebral oxygen consumption parallel each other during hypothermia, but direct measurements of cerebral metabolism were not made. It therefore seemed appropriate to investigate the influence of hypothermia on this and other functions of the nervous system; I shall present the results of such a series of experiments.

The general procedure was the same in all of these studies. The experimental animals were mongrel dogs which were unselected as to age and sex. Anæsthesia was achieved solely by the use of intravenous sodium pentobarbital, 30 mg./kg. The dogs were intubated, and respiration was controlled continuously with an automatic, positive-negative pressure, closed-system respirator, which delivered 100% oxygen at a rate of 24 respirations per minute. The respirator was adjusted to maintain a tidal volume of 200–400 ml., as measured from a spirometer. Temperature readings were obtained from a thermistor inserted 200 mm. into the œsophagus. Hypothermia was induced by immersion to the shoulders in ice water.

Attention was directed first toward the effect of hypothermia on cerebral vascular dynamics and cerebral metabolism (Rosomoff and Holaday, 1954). This necessitated the development of a method for measuring the cerebral blood flow of the dog. Such a technique was perfected.

The effect of hypothermia on the cerebral blood flows of 10 dogs is depicted in Fig. 1. Body temperature during the pre-cooling control period was usually between 35° and 36° C. In order to facilitate comparative analysis of the data, values at 35°, interpolated when necessary, were designated as 100% at the control level. The blood flows of individual animals, expressed as a percentage of the flow observed at 35°, were plotted against temperature. Cerebral blood flow varied proportionately with changes in temperature.

Systemic blood pressure was measured simultaneously with the determination of cerebral blood flow from a catheter in the aorta. When the mean blood pressure and blood flow of a circulatory system are known, the vascular resistance may be calculated. The relationships of these factors during hypothermia are illustrated in Fig. 2. As temperature was reduced, average cerebral blood flow decreased in a linear fashion, at a rate of 6·7% per °C. Average mean blood pressure decreased in a similar manner, but at a slower rate, 4·8% per °C. Average cerebral vascular resistance increased; however, this function exhibited considerable variability (Rosomoff, 1956*a*). It was interesting to note that even though average blood pressure showed a steady decline as temperature was reduced, individual determination at each temperature level demonstrated large oscillations, as compared to the cerebral blood flow which fell relatively constantly. Cerebral vascular resistance, therefore, must have changed considerably in order to maintain the constancy of blood flow in the face of a fluctuating blood pressure. Hence, it seemed likely that cerebral vascular tone was actively regulated at all temperatures down to 25° C., probably as a function of the respiratory gas tensions in the brain.

As cerebral blood flow was measured, periodic blood samples were drawn for the analysis of cerebral arterial and venous oxygen contents. The arterial source was the internal carotid artery, the venous source was the superior sagittal sinus. Cerebral oxygen consump-

[1]The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

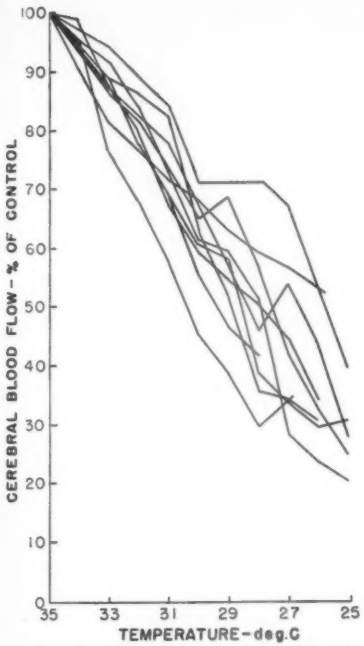

FIG. 1.—Each line represents cerebral blood flows of one animal between 35° and 25° C. expressed as percentage of flow observed at 35° C. (Rosomoff and Holaday, 1954.)

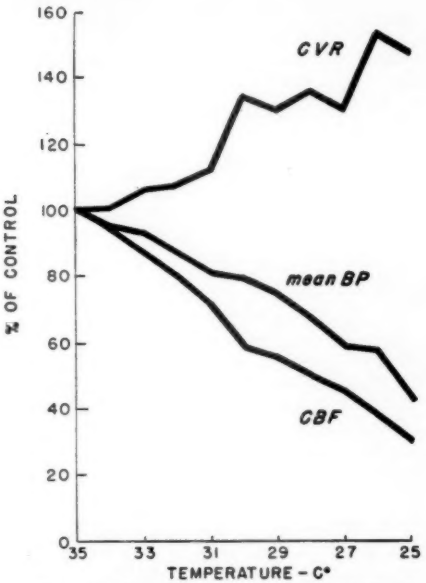

FIG. 2.—The relationships of cerebral blood flow, mean blood pressure, and cerebral vascular resistance during hypothermia. (Rosomoff, 1956*a*.)

tion was then calculated as the product of the cerebral blood flow and the arteriovenous oxygen difference. Cerebral blood flow decreased as the temperature was reduced, while the arteriovenous oxygen differences remained almost unchanged. Therefore, cerebral oxygen consumption must have decreased at the same rate as blood flow. In Fig. 3 the mean cerebral blood flow and oxygen consumption of four dogs were plotted with their control values adjusted to the same level. It can be seen that cerebral blood flow and cerebral oxygen consumption decreased at the same rate with decline of temperature, so that at 25° C., both were one-third of the pre-cooling level. These results were recently confirmed in man by Stone and his co-workers (1955) using the nitrous oxide method of Kety. *In vitro* determinations of brain slice metabolism also show a decrease in oxygen consumption with reduction of temperature, and exhaustive histologic studies have failed to demonstrate any evidence of cellular damage (Field *et al.*, 1944; Lougheed and Kahn, 1955). Therefore, it is probable that hypoxia of the brain does not occur during hypothermia in this temperature range, so long as adequate respiratory and circulatory functions are maintained.

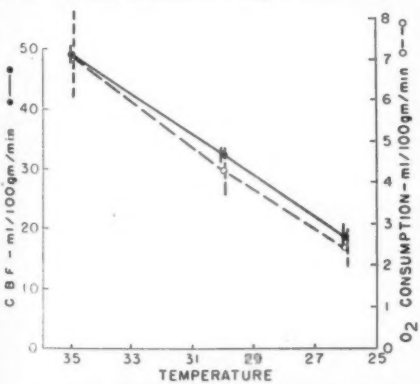

FIG. 3.—Solid circles joined by solid lines represent mean cerebral blood flows of four animals at 35°, 30° and 26° C. Open circles joined by broken lines represent mean cerebral O_2 consumption of the same animals. Vertical lines represent standard error of each mean. (Rosomoff and Holaday, 1954.)

It was noted during these experiments, that the brain appeared smaller at 25° C. than at normothermic levels. Studies were conducted in an attempt to verify this observation and to quantitate the degree of change (Rosomoff and Gilbert, 1955). Brain volumes were determined by the method of White and his co-workers (1942).

The brain volumes of four dogs were determined at 37° C. in order to establish control values, as shown in Table I. At this temperature, the differential index of brain volume was

TABLE I.—ESTIMATED BRAIN VOLUMES, CRANIAL CAPACITIES, AND DIFFERENTIAL INDICES OF BRAIN VOLUME OF FOUR NORMOTHERMIC DOGS (37° C.) (Rosomoff and Gilbert, 1955)

No.	Brain volume (ml.)	Cranial capacity (ml.)	Differential index of brain volume (%)
105	69·9	78·1	10·5
109	67·1	75·6	11·3
110	70·1	79·3	11·7
111	62·3	69·7	10·6
Mean			11·0

11%, indicating that the brain occupied 89% of the cranial capacity of the normothermic dog, while the extracerebral space, meaning that intracranial space not occupied by brain, was 11% of the total.

With the normothermic values established, the process was repeated in 9 dogs with body temperatures of 25° C. The percentage change of brain volume and extracerebral space were calculated, as indicated in Table II. Assuming that the relative sizes of the brains of the

TABLE II.—DIFFERENTIAL INDICES OF BRAIN VOLUME, CHANGES IN EXTRACEREBRAL SPACE, AND CHANGES IN BRAIN VOLUME OF NINE HYPOTHERMIC DOGS (25° C.) (Rosomoff and Gilbert, 1955)

Dog No.	Differential index of brain volume (%)	Change in extracerebral space (%)	Change in brain volume (%)
102	18·6	+68·9	−8·5
104	13·9	+26·3	−3·3
106	14·6	+32·2	−4·0
108	13·6	+23·8	−2·9
112	15·0	+36·2	−4·8
113	14·2	+28·6	−3·5
115	15·7	+42·4	−5·3
116	14·0	+27·0	−3·3
117	12·1	+ 9·9	−1·3
Means	14·4	+31·8	−4·1

experimental dogs prior to the induction of hypothermia were equal to those of the controls, then at 25° C., their brain volumes must have decreased 4·1%. As a result, the extracerebral space increased 31·8%. This is equivalent to 3 ml. in the average 10 kg. dog. If a similar change were to occur in man, it would amount to 55 ml. in the average adult.

The effect of hypothermia on cerebrospinal fluid pressure and venous pressure.—The cerebrospinal fluid pressures and venous pressures were recorded from needles in the cisterna magna and jugular vein, respectively. The dog was in the lateral, horizontal, recumbent position.

The individual cerebrospinal fluid pressures of nine dogs are plotted in Fig. 4. Each is expressed as the percentage of the pressure observed at 37° C. There was an inconstant initial response to the application of cold. In five animals, the cerebrospinal fluid pressure increased; in four animals, a decline was observed. Thereafter, there was a progressive decrease in cerebrospinal fluid pressure with reduction of temperature in all animals. The average decrease of cerebrospinal fluid pressure per degree decline of temperature between 37° and 25° was 5·6% of the control value.

In Fig. 5, the average cerebrospinal fluid pressures and venous pressures were plotted simultaneously. Both varied as a function of temperature. Again, the initial increases in pressure were noted. These increments coincided directly with the appearance of shivering. When shivering did not occur or when it was eliminated by supplementary doses of pentobarbital, no increase in either pressure was noted. This indicates the need for proper and adequate anæsthesia during the induction of hypothermia.

To recapitulate, then, hypothermia has the following effects on the normal physiology of the nervous system. These are: (1) a decrease in cerebral blood flow; (2) a corresponding reduction in cerebral metabolism; (3) an induced and compensated hypotension; (4) an increase in cerebral vascular resistance; (5) a decrease in brain volume; and (6) a diminution of intracranial pressure and venous pressure.

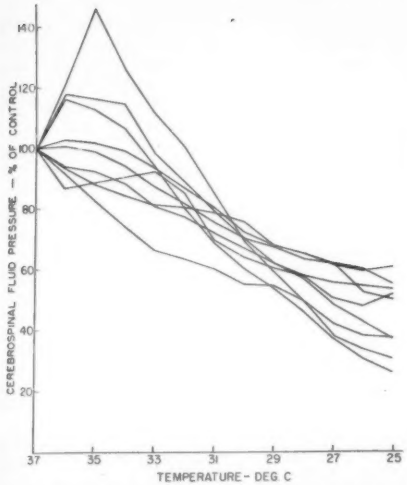

FIG. 4.—Each line represents the cerebrospinal fluid pressures of one animal between 37° and 25° C. expressed as percentage of the pressure observed at 37° C. (Rosomoff and Gilbert, 1955.)

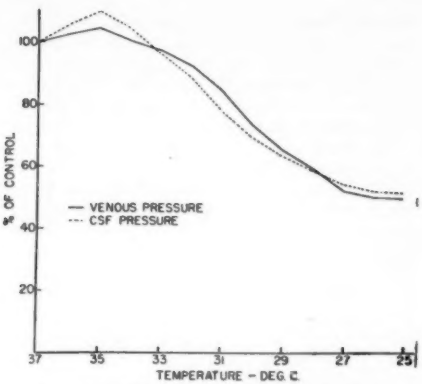

FIG. 5.—Solid line represents the mean venous pressure of five animals between 37° and 25° C. expressed as percentage of the pressure observed at 37° C. Broken line represents the mean cerebrospinal fluid pressures of five animals between 37° and 25° C. expressed as percentage of the pressure observed at 37° C. (Rosomoff and Gilbert, 1955.)

The effect of hypothermia on some abnormal physiology of the nervous system.—It has been well established that permanent occlusion of the middle cerebral artery in the normothermic dog produces an area of infarction of significant magnitude (Evans and McEachern, 1938; Hain *et al.*, 1952; Petersen and Evans, 1937; Rasmussen, 1938). This is proportional to the degree and to the rapidity of the occlusion (Harvey and Rasmussen, 1951). It was postulated that a marked reduction of cerebral metabolism at the time of the occlusion would provide more advantageous conditions for the establishment of collateral circulation, thereby resulting in the modification or prevention of infarction. It was thought that such conditions might be attained with the use of hypothermia (Rosomoff, 1956*b*).

In these experiments, the method for inducing hypothermia was the same as previously described. The left middle cerebral artery of the dog was exposed through a subtemporal craniectomy: it was interrupted at its origin at normal body temperature in one group of animals, and during hypothermia in a second group.

Interruption was produced by one of three separate procedures. One was a simple transection at the origin. A second was what I have called a "crotch isolation", which is a transection of the middle cerebral artery combined with clip occlusion of the ipsilateral internal carotid, anterior cerebral, and posterior communicating arteries. The third procedure was a segmental resection of the middle cerebral artery from its origin to the first major cortical bifurcation.

After closing the wound the hypothermic dogs were immediately rewarmed in a water bath in which the temperature was maintained 10° C. higher than that of the dog, until normothermic levels were attained. The total period of hypothermia following interruption of the artery was three hours. The first hour was spent in deep hypothermia, 22–24° C.; the remaining two hours were spent at increasingly higher levels as part of the rewarming phase. Both normothermic and hypothermic animals were observed for eighteen to twenty-two days, and then they were sacrificed. The brains were removed for gross and microscopic study. All neurological abnormalities were charted daily, and a neurological score was computed for each animal.

The sum total of our experience is shown in Table III. 14 of the 15 normothermic dogs

TABLE III.—INTERRUPTION OF THE MIDDLE CEREBRAL ARTERY IN THE DOG AT NORMAL BODY TEMPERATURE AND DURING HYPOTHERMIA (22–24° C.)

Degree of change	15 Normothermic dogs		15 Hypothermic dogs	
	Neurological	Pathological	Neurological	Pathological
Severe ..	11	11		
Moderate ..	3	3		3
Minimal ..		1	5	10
None ..	1		10	2

showed moderate to severe abnormal neurological signs on clinical examination; one dog had no detectable abnormalities. In general, the severity of pathological change was commensurate with the neurological manifestations, except in the case of the single animal that had no clinical aberrations. That animal developed minimal pathological involvement, namely, infarction of the basal ganglia structures and a small portion of the adjacent internal capsule which produced no clinically detectable signs.

By contrast, the hypothermic dogs showed a marked reduction of both neurological and pathological manifestations. Only 5 of the 15 hypothermic dogs evidenced abnormal neurological signs. When such signs were present, they were minimal in degree and transient, none persisting past the sixth post-operative day. The remaining 10 animals developed no demonstrable clinical abnormalities. Post-mortem studies revealed a higher incidence of pathological change than would have been predicted from the dogs' clinical appearances. All but two animals developed evidence of infarction; however, these infarcts were small, some being detectable only on microscopic examination. The paucity of clinical manifestations can be explained by the small size, and by the restriction of the lesions to relatively "silent areas"; i.e. portions of the basal ganglia, anterolateral internal capsule or thalamus, and hypothalamus.

Coronal sections of the brain of a normothermic dog that had middle cerebral artery transection are shown in Fig. 6. Marked distortion and disruption of the architecture are

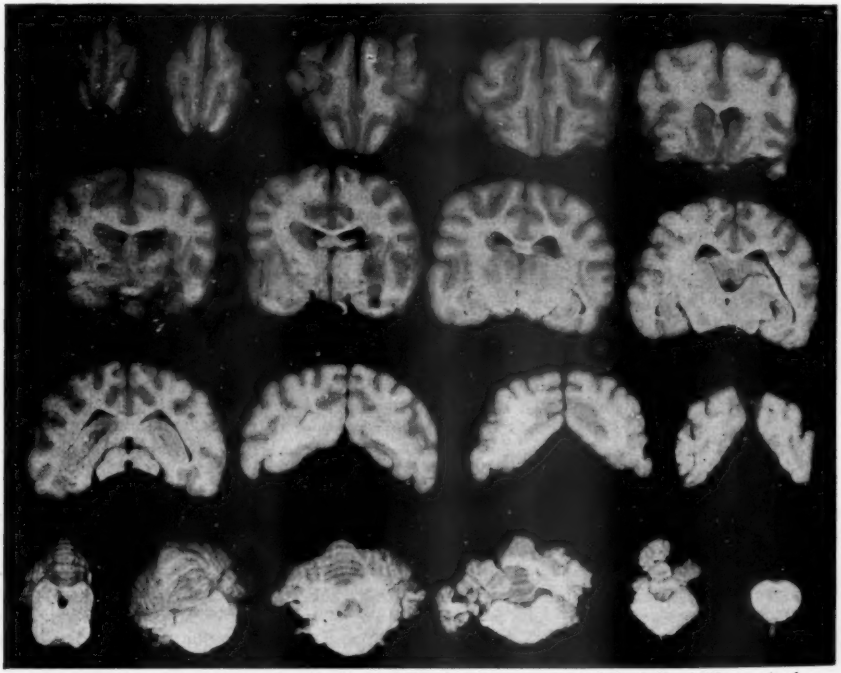

FIG. 6.—Coronal sections of a dog brain following interruption of the left middle cerebral artery at normal body temperature.

seen which involves the basal ganglia, internal capsule, thalamus, hypothalamus, visual pathways, and parts of the overlying fronto-parieto-temporal cortex.

Coronal sections of the brain of a hypothermic dog subjected to the same procedure are demonstrated in Fig. 7. This brain was intact, except for two areas: some post-traumatic changes in the ectolateral gyrus due to retraction during the operation, and a small infarct ($1 \times 3 \times 4$ mm.) in the centrum semiovale.

The film documents the clinical appearance of a group of normothermic dogs and their hypothermic equivalents, following interruption of the middle cerebral artery.

Interruption of the middle cerebral artery in the normothermic dog produces a triad of clinically detectable neurological manifestations. These are: (1) ipsilateral forced circling movements, (2) a

contralateral hemiparesis, and (3) a contralateral temporal homonymous visual field defect. Five pairs of animals, one normothermic and one hypothermic dog per pair, were photographed at the 1st, 3rd, 7th, 14th and 21st day of their post-operative course. The normothermic dogs all demonstrated the triad of neurological signs. By contrast, the hypothermic dogs manifested little or no abnormal neurological signs.

There was no doubt that hypothermia did exert a protective influence in the dog, following interruption of the middle cerebral artery. It was therefore concluded that hypothermia protects against cerebral infarction in the dog.

How might this information be applied clinically to man? The list of advantages derived from hypothermia is impressive. Those shown in Table IV appear to be particularly well

TABLE IV.—ADVANTAGES DERIVED FROM HYPOTHERMIA

1. Decrease in cerebral blood flow.
2. Corresponding reduction of cerebral metabolism.
3. Induced, compensated hypotension.
4. Decrease in brain volume.
5. Diminution of intracranial pressure.
6. Safety factor against the consequences of prolonged temporary or permanent interruption of major vascular channels.

adapted for use in the treatment of many problems peculiar to diseases of the nervous system, especially problems related to pathology of the vascular elements, and those coincident to the expansion of mass lesions.

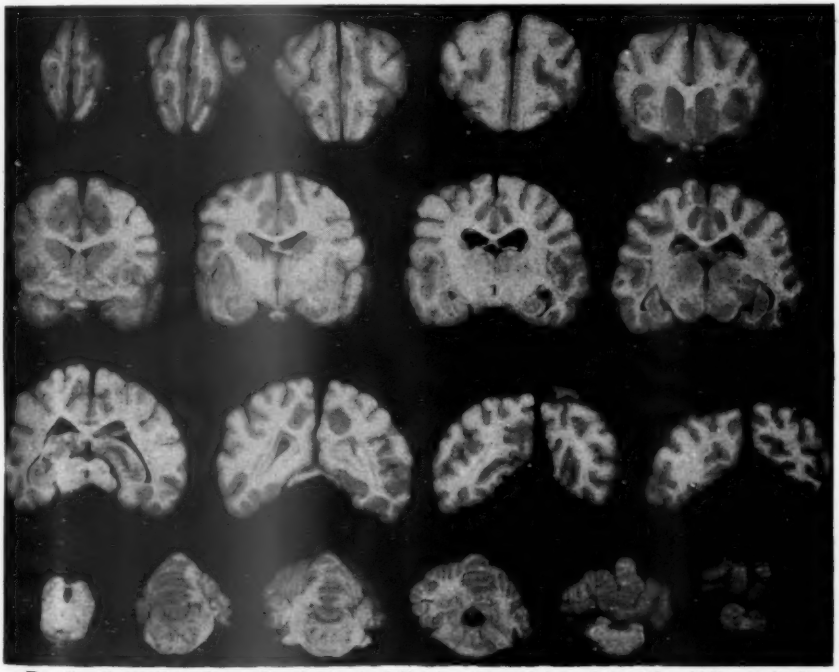

FIG. 7.—Coronal sections of a dog brain following interruption of the left middle cerebral artery during hypothermia.

We have had the opportunity to use this technique in man in a small number of cases, as an adjunct to the intracranial surgery of cerebral vascular anomalies. Intracranial surgery in the treatment of cerebral vascular anomalies has been sharply limited by numerous hazards attendant on such procedures. Not only is the task of achieving hæmostatis frequently difficult, but it is often made more formidable by the risk of producing a neurological deficit consequent to the interruption of a major vascular channel. We therefore used hypothermia in these cases with the hope that it would enable us to perform definitive and curative surgery for many lesions which now are commonly considered inoperable.

To date, our faith in this technique appears to have been justfied. Cerebral blood flow

was reduced, which facilitated hæmostasis. The brain was "slack": manifestations of the decreased brain volume and decreased intracranial pressure. Surgery was technically easier, more expeditious, and performed with a minimum of trauma. In each instance, the result was a successful extirpation of the lesion. The necessity for occluding a singular major cerebral vessel has not yet arisen, so this portion of the thesis has not been tested in man. However, the cardiac surgeons have amply demonstrated that cerebral circulation can be temporarily interrupted for extended periods without incurring a neurological deficit.

For the present, we have limited our activities to the treatment of cerebral vascular anomalies; however, there is every reason to believe that hypothermia will prove valuable in the treatment of other neurological problems related to the physiological processes which I have described. Hypothermia has much to offer the clinician who treats neurological diseases, as well as providing an additional tool for studying cerebral function both in health and disease.

ACKNOWLEDGMENTS.—Figs. 1, 3, 4 and 5, and Tables I and II, are reproduced from the *American Journal of Physiology*, and Fig. 2 from *Surgery*, by kind permission.

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Dr. B. A. Cookson (Surgical Unit, University College Hospital Medical School, London):

The Cardiac Effects of Certain Hypotensive Drugs and Muscle Relaxants In Hypothermia

One of the cardinal characteristics of the hypothermic state is a slowing of the pulse. Thus at a rectal temperature of 26° C. (79° F.) the heart rate in the dog is approximately halved (120/min. to 60/min.) and at 20° C. it is quartered (30/min.) At an average temperature of 19° C. a dramatic event takes place (Cookson and DiPalma, 1955), the heart rate suddenly drops to 1/20 of its normal speed (6/min.). This abrupt change in rate (*see* Fig. 1) is usually associated with a disappearance of the P wave from the electrocardiogram. The heart is now in nodal rhythm. The blood pressure falls to a negligible level and the veins become engorged.

It was at first thought that this severe bradycardia (19° C.) might be due to excessive vagal tone. However, the dubious results of vagal section and the completely negative effects of the exhibition of a large dose of atropine made this hypothesis unfeasible. It was concluded therefore that the severe bradycardia was due to a direct effect of cold on the sino-atrial node.

Since atropine and vagotomy were unsuccessful the possibilities of adrenaline were investigated. This in doses of 10γ/kg. intravenously produced an immediate relief of the severe bradycardia and at the same time restored the P wave to the electrocardiogram. Thus the heart rate which before was as slow as 5/min., became, two to three minutes after adrenaline, as fast as 40/min. However, 50% of the animals given this dose of adrenaline went into ventricular fibrillation shortly after the initial cardiac acceleration.

The most unexpected discovery was that quaternary nitrogen compounds of the muscle relaxant and ganglionic blocking agent groups were capable of relieving the severe bradycardia at 19° C.—the heart rate increasing up to 20–40 beats/min. (Cookson and DiPalma, 1955, unpublished data). The following drugs were found to be capable of relieving bradycardia in hypothermic dogs,[1] probably as a result of their direct effect on the sino-atrial node: Hexamethonium chloride (C6) 20–25 mg./kg.; Tetraethylammonium chloride (T.E.A.) 7·5–75 mg./kg.; Tetrabutylammonium iodide (T.B.A.) 5–12·5 mg./kg.; *d*-Tubocurarine 2 mg./kg.; Flaxedil 10–12 mg./kg.

Therapeutically these drugs are disappointing, since the relief of the bradycardia is frequently followed by ventricular fibrillation. However, this undesirable side-effect occurs

[1]It is of interest to note that tetramethylammonium iodide (T.M.A.) and choline in doses up to 100 mg./kg. were unable to relieve the severe bradycardia.

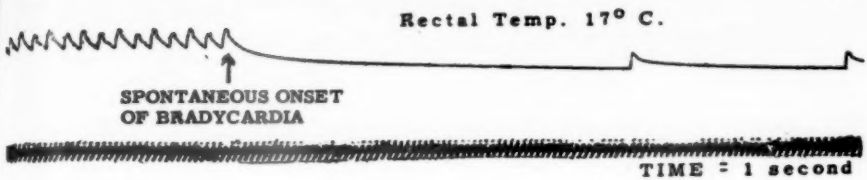

FIG. 1.—Pulse and ECG changes in severe bradycardia. Pulse tracing shows the acute onset of bradycardia, while the ECG records show a change from sinus to nodal rhythm. From Cookson, B. A., and DiPalma, J. R. (1955) By kind permission of the *American Journal of Physiology*.

only occasionally in the case of hexamethonium. A further consideration is that most of the drugs used are only effective in doses considerably in excess of those ordinarily needed to produce ganglionic or neuromuscular blockade. From a practical point of view there would seem to be no cast-iron contra-indication to the use of these drugs in clinical hypothermia provided the anæsthetist (1) does not employ large doses; (2) avoids the hazard of the drugs accumulating in the hypothermic state; (3) is aware that any cardiac acceleration resulting from the use of these drugs may be potentially dangerous (ventricular fibrillation).

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Mr. D. N. Ross (Guy's Hospital): *Principles Underlying the Application of Hypothermia to Cardiac Surgery*

It has been our aim to establish a practical and safe method of hypothermia which will permit cardiac surgery under dry-heart conditions. We have not felt justified in using the technique unless an arrest of the circulation has been involved.

In our dog experiments we tried to establish the rough limits of safety of the procedure and since that time, by combining our clinical and experimental knowledge, we have arrived at a number of conclusions which guide us in the management of our cases.

Many alterations of body physiology have been observed, not all of which are of obvious practical importance at this stage but it is clear that the physiology of hypothermia deserves detailed study. In particular, it must be established that the changes observed are truly physiological and wholly reversible with no permanent alteration of cell function or structure. In this respect it has been our experience that prolonged hypothermia is unlikely to be followed by recovery and this may be related to the occurrence of irreversible changes in the cells. In dogs, where cooling has been followed by immediate rewarming, recovery has been the rule but where the hypothermic state has been maintained, the percentage of recoveries has fallen steeply after three to five hours of hypothermia (Fig. 1). This increased mortality has been associated with marked changes in physiology, particularly the development of uncontrollable oozing, a progressively falling blood pressure and cardiac output, abnormal fluid shifts and the well-known but ill-understood picture described as a "rewarming death".

Fisher and his associates (1955) have recently published a series of careful physiological observations made on dogs during deliberately prolonged hypothermia, and they confirm many of our findings.

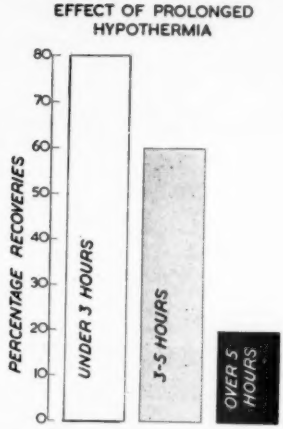

FIG. 1.—The effect of prolonged hypothermia on the recovery rate in dogs.

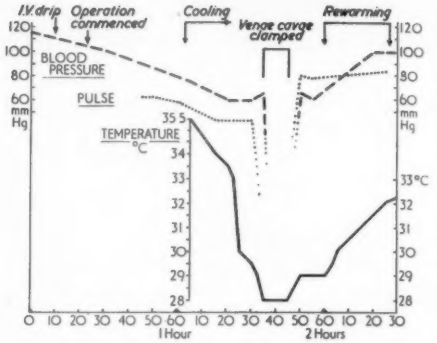

FIG. 2.—Graph made at operation. Period of hypothermia is less than two hours.

Consequently we now feel that rapid cooling within an hour followed by a short intracardiac procedure and immediate rewarming is the first requirement of a successful clinical result. This we achieve by delaying our cooling until the chest has been opened and the diagnosis has been confirmed. We then cool and rewarm rapidly by the venous bloodstream method (Ross, 1954*a*). By instituting blood-stream rewarming immediately after the period of circulatory arrest and while the chest is being closed, uniform rewarming of the superficial and deep tissues begins immediately and the temperature is near normal by the end of the operation. In this way the total period of significant hypothermia need not, as a rule, be greater than two hours (Fig. 2).

In common with other workers we have found that the greatest disadvantage of the hypothermic method has been the onset of ventricular fibrillation during cooling, generally with little electrocardiographic or other warning. When the patient is cool the problem is not urgent since the brain is then protected against anoxic damage for some time. We recognize that it is the ventricular fibrillation occurring during cooling which constitutes the greatest danger and for this reason we believe it is necessary to have the chest open and the heart under vision during the induction of cooling. With the heart in view, disturbances of rhythm are immediately detectable and resuscitative measures can be employed without delay.

With regard to the causes of the ventricular fibrillation under hypothermic conditions, we have little to contribute but in their prevention, we avoid all mechanical trauma during the cooling since all manipulation of the heart necessary for confirmation of the diagnosis has been completed at normal temperature when the heart is in a non-irritable state. A falling cardiac output has been noted in our dogs (Ross, 1954*b*) and since this is associated with a diminished coronary blood flow, an attempt is made to maintain the coronary perfusion pressure by means of a very slow drip of noradrenaline aimed at maintaining a systemic blood pressure of 80 mm. of mercury. Prostigmin is used during the intracardiac surgery as advocated by Montgomery *et al.* (1954) but we have not found that this will invariably prevent ventricular fibrillation. Riberi *et al.* (1955) have suggested that infiltration of the sino-auricular node with procaine will prevent the onset of fibrillation. Although we have no clinical experience of this deliberate blockage of the pacemaker, our incidence of ventricular fibrillation appears to be less and our ability to resuscitate greater in those hearts in which auricular fibrillation has occurred earlier in the cooling; in other words, after control of the ventricles by the sino-auricular node has been lost. This observation is being investigated further.

In the treatment of established fibrillation occurring during the intracardiac manipulations, we have established a firm principle. We ignore the disturbance, complete the correction of the intracardiac defect and release the circulation before attempting resuscitation. By correcting the shunt or stenosis within the heart first, the circulation is immediately improved with a correspondingly better chance of effecting successful defibrillation.

Many workers have commented on the difficulty in defibrillating hypothermic hearts.

This has not been our experience provided we first correct the intracardiac defect, then massage the heart to restore tone and vigorous fibrillary movements before attempting electrical defibrillation. In our hands, the restoration of myocardial tone is undoubtedly best achieved by means of the intracardiac injection of 1/10,000 adrenaline. We would agree that adrenaline may precipitate ventricular fibrillation during cooling but once the arrhythmia is established, it is undoubtedly the drug of choice prior to electrical defibrillation. It will be remembered that blood-stream rewarming will have been started by the end of the cardiotomy and this further increases the chances of defibrillation in the rewarming heart.

An increased bleeding tendency in hypothermic tissues undergoing surgery is a common experience and we have been able to correlate this with an initially reversible increase in the clotting time of blood brought about by the physical action of cold. This prolongation of the clotting time has been turned to advantage in the venous cooling method in that it enables us to dispense with the use of heparin in the extracorporeal cooling circuit. Rewarming restores the clotting time to normal in the uncomplicated case. A different picture is presented by the persistent and irreversible oozing found after prolonged hypothermia induced by either the surface or blood-stream methods. This was noted in a number of our dogs and in earlier clinical cases. We have not been able to explain this adequately on the basis of a loss of blood platelets nor as a result of excess of transfused citrated blood and it has been suggested that it may be due to interference with prothrombin formation in impaired or damaged liver cells resulting from too long a period of reduced body temperature. We believe that a short hypothermic period has helped to abolish this bleeding tendency but it is also our invariable practice to transfuse our patients at the end of their operations with blood freshly collected from a donor on the morning of operation.

Control of the rate and depth of cooling can only be achieved with accuracy as far as we are aware by a blood-stream cooling method since there is then no uncontrolled downward drift of temperature after the cooling stops (Fig. 3). Many experiments have been performed

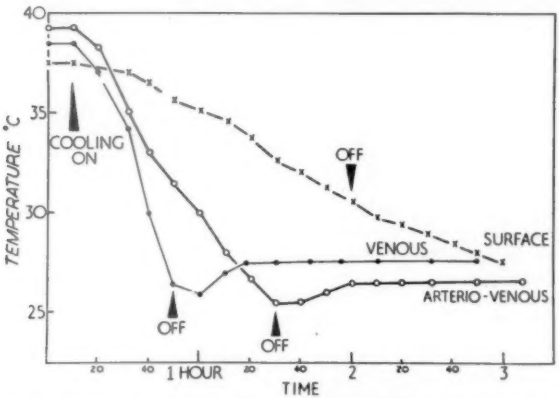

FIG. 3.—Comparison of different cooling methods in the same dog. Note afterdrop of temperature in surface cooling.

to determine the best site and the best instrument for the recording of body temperature. The result has been that we now use an ordinary glass centrigrade thermometer and the anæsthetist records temperatures at five- to ten-minute intervals from the pharynx. The recording of rectal temperatures is definitely misleading in blood-stream cooling since this temperature lags far behind pharyngeal, heart, blood and œsophageal temperatures. Pharyngeal temperatures are convenient to record and they probably reflect the temperature of the tissues supplied by the carotid arteries including the brain. Our choice of the ideal temperature to which to cool has been based upon studies of oxygen consumption and dog survivals after occluding the cerebral vessels at various temperatures. Our findings have been in conformity with those of others and we have felt that at 25° C. we can afford fifteen minutes of cerebral ischæmia. However, in view of the undoubtedly increased tendency to myocardial irritability and fibrillation below 30° C. we have arrived at a compromise temperature of 27° C. to 28° C. allowing ourselves about 10 min. of arrested circulation but this has been prolonged to 12 min. without ill-effect.

Finally, although it is well known that very young mammals are better able to tolerate

low body temperatures, age has not been a significant factor in determining the outcome in our clinical cases. More than half of those operated upon with a successful outcome have been adults.

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Dr. E. J. Delorme: Comparative physiology has already presented us with a number of clues in the study of hypothermia in man and more may yet be learned from these experiments of nature, particularly from the adaptations seen in the hibernator, the diving mammal and the responses of temperate and arctic animals to cold.

In clinical studies, contradictory evidence has appeared on (1) the antagonistic role of potassium and calcium ions in the disordered action of the cooled heart; (2) the value of carbon dioxide narcosis during hypothermia and (3) the aggravating or protective influence of cold on shock.

A plea is made for some conformity in the recording of temperatures with the recommendation that mid-œsophageal temperature readings be adopted.

In prospect, the following developments are foreseen: a wider use of light hypothermia (range 35–30° C.); a restriction in the use of moderate hypothermia (range 30–25° C.) to conditions where interruption of the circulation is required; more effective measures for controlling cardiac arrhythmias; the safe attainment of deep hypothermia (range 25–12° C.) by means of cooling through pump oxygenators.

Mr. Bernard Fisher: Apropos the comments concerning Phyllis Knocker's article on "Effects of Experimental Hypothermia on Vital Organs", appearing in the *Lancet* (1955, ii, 837), I should just briefly like to present some of our findings on the effects of prolonged hypothermia at 22°–24° C. upon hepatic physiology in the dog. This work was done in the Surgical Research Laboratories at the University of Pittsburgh.

During hypotension the bile volume was markedly decreased as was the total amount of cholic acid. After rewarming the length of time required for these volumes to return to normal depended upon the length of hypothermia. After six hours of cooling the pattern of biliary secretion was similar to that following one hour of open drop ether anæsthesia. By eighteen to twenty-four hours the volume of bile and content of cholic acid had returned to normal. Following twelve hours of hypothermia it took about thirty to thirty-six hours for return to pre-cooling levels.

Hypothermia up to six hours produced no decrease in the *in vitro* oxygen consumption of the liver slice. Longer periods did produce a significant decrease in this value, but even after twelve hours of hypothermia there was a prompt return to normal or above normal levels of consumption.

In so far as the effect of hypothermia upon the composition of the liver is concerned aside from an increase in the NPN fraction and a marked decrease in glycogen, no other alterations were found.

Measurement of hepatic blood-flow up to twelve hours of hypothermia showed a significant decrease, which, following rewarming, promptly returned to normal.

From these and other observations we concluded that hypothermia maintained for as long as twelve hours produced no apparent irreversible changes in the liver.

Dr. I. K. R. McMillan: I have recently, in association with Drs. R. Case and L. W. Stainsby, been studying the function of the ventricles in hypothermia. This work was carried out at the National Heart Institute, Bethesda, Maryland, U.S.A. in Dr. S. J. Sarnoff's laboratory.

In our experiments the function of the ventricles is nearly always as good at 28° C. as it is at 37° C. This is best expressed in terms of the stroke work of the ventricle under study, which can rise as high as in normothermia when an increased work load is put upon it. The slowing in pulse rate is probably one factor in enabling the heart to reach these high stroke works.

While this does not in any way help in solving the problem of the origin of ventricular fibrillation in hypothermia it does mean that the capacity of the heart muscle to contract in face of high filling and systemic pressures is not reduced under these conditions.

We also measured flow in the left coronary artery under hypothermia and noted the steady fall reported by other workers. The decrease of coronary flow was greater than the simultaneous fall in systemic pressure, in that coronary flow fell by 80% while the systemic pressure only fell 33%, suggesting that the decreased coronary flow requirements in hypothermia to maintain a systemic pressure, might well be of value in relation to surgery.

BOOK REVIEWS

Diseases of the Nervous System. By Sir Russell Brain, Bt., D.M., P.R.C.P. 5th edition. (Pp. xviii + 996; illustrated. 55s.) London: Oxford University Press (Cumberlege). 1955.

The fifth edition of this well-known text is assured of the welcome its predecessors have enjoyed. It is written in the sound tradition of British clinical texts: that is, it deals adequately and systematically with the features and the courses of the illnesses it describes, and does not sacrifice this first and vital approach to the many ancillary diagnostic methods now available: methods only safely to be employed after clinical analysis has been made.

This edition is an impressive tome of close upon 1,000 pages. Yet, even so, so numerous are the clinico-pathological aspects of nervous disease that many affections receive a notice so brief as to be scarcely of informative value, while of the more common and important maladies not all receive the consideration their incidence merits.

The problem as to what is the optimum scale for a work of reference is not an easy one, but it is probable that the two-volume dimensions of Kinnier Wilson's classic but unfinished work, represents the minimum, and since this work is essentially a period piece, we have not now in any language a modern work of reference in neurological medicine.

Nevertheless, within the limits he has set for himself the author has covered the subject with success, if, perhaps, in a somewhat schematic fashion that hides from the reader the sense of personal experience and clinical flair that are so necessary to bring a textbook really to life.

Thus, this is a most admirable book for the candidate for a higher examination. He will find therein all that any reasonable examiner could ask, with no hint of anything in the least controversial or individual that the most sensitive of this sensitive tribe could object to.

Yet, after all, there are differences of opinion and of judgment in clinical neurology as in all other aspects of medicine, and to reduce the account of disease to a common factor of general agreement is to oversimplify, and to invite the criticism of dullness.

For example, an adequate answer to an examination question upon cerebral thrombosis could be compiled from these pages, but there is insufficient indication in them, it may be urged, of the perplexities that in many cases of this illness beset the making of a prognosis for as long as two or three weeks: e.g. the wide fluctuations in consciousness, in blood pressure, in degree of hemiplegia, bladder control and so on, that occur in unpredictable sequence in so many cases.

A comparable remoteness from clinical reality invests the too brief account of acute febrile polyneuritis. The author says that slight cardiac dilatation may occur and that the patient may die from paralysis of respiratory muscles. There is no hint of the fact that many such cases die from cardiac failure and not from paralysis of muscles; no account of the picture of a rapidly rising pulse, progressive cardiac dilatation, pulsating jugulars leading to sudden death, no adequate hint of the terrible urgency that may attend the care of such a case.

It would be nice to see an adequate description of the Jacksonian convulsion, which is far more varied and striking than modern textbooks reveal, or clinicians realize.

The relation of trauma to nervous disease has always been a dimly-lit field of debate, but the student of Cushing and Eisenhardt's classic monograph (1938) on the meningioma knows that Cushing has provided the most weighty and fully-documented evidence in favour of the striking relation between certain types of head injury and the development of meningiomas at the bregma and the pterion. To dismiss all this in a sentence by saying that "rarely" a meningioma may occur beneath a head injury is inadequate and misleading.

These are, perhaps, but minor criticisms of a book the popularity of which vindicates its wide usefulness. Every author writes the book that is in him and not any other, and here the author following the convention of a certain remoteness in his treatment of his subject, and a disinclination to stress the difficulties and obscurities of clinical neurology, has provided a lucid and well-written account, but one informed perhaps by a keener sympathy for the examination candidate than for the doctor struggling with the burdens of diagnosis and treatment at the bedside.

An Introduction to Pool Exercises. By Elizabeth Bolton, M.C.S.P., H.T. and Diana Goodwin, M.C.S.P., H.T. Foreword by J. W. T. Patterson, M.D., F.R.C.P.Ed. (Pp. 48; illustrated. 5s.) Publishers: E. & S. Livingstone Ltd. 1956.

Pool therapy is an accepted and time-honoured method of treating the results of diseases of the locomotor system in which muscular weakness is an aftermath. Such diseases include not only rheumatoid arthritis and osteo-arthritis, but the later effects of poliomyelitis also. For this reason there is an increasing demand in hospitals treating these disabilities for remedial pools, and also for physiotherapists competent to use them to maximum advantage.

The authors have presented in this small volume all that it seems necessary to know on the subject, and have illustrated their thesis with quaint but effective little diagrammatic sketches.

Local Analgesia: Head and Neck. By Sir Robert Macintosh, D.M., F.R.C.S.(Edin.) F.F.A.R.C.S., M.D. (hon. causa) Buenos Aires and Aix-Marseilles, and Mary Ostlere, M.B., M.R.C.P.E., F.F.A.R.C.S. (Pp. viii+138; 145 figs. 27s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

This excellently produced monograph is divided into two sections, the longer of which is devoted solely to anatomy. Both parts are illumined by numerous clear and original drawings (by Miss Marjorie Beck) which admirably amplify the brief and concise text.

It is not a comprehensive reference book as few alternative techniques are described and there is little discussion of general principles. However, this deficiency is more than offset by the Authors' practical outlook, for the methods they so clearly detail are sufficient for most surgery and, in their own words "have been found useful".

This monograph maintains the high standard set by its predecessors from Professor Macintosh's Department of Anæsthetics, and can be recommended not only to practising anæsthetists and surgeons but also to candidates for the Diplomas in Anæsthetics.

Cardiovascular Surgery. Studies in Physiology, Diagnosis and Techniques. Proceedings of the Symposium held at Henry Ford Hospital, Detroit, Michigan, March 1955. Edited by Conrad R. Lam, M.D. (Pp. xxix + 543; illustrated. 89s.) Philadelphia and London: W. B. Saunders Company. 1955.

This volume contains material which was presented during two and a half days by 60 speakers who met to discuss the surgery of cardiovascular disease. The foreword to the symposium is written by Sir Russell Brock. The remarks that follow in this review are meant to emphasize certain truisms, and some pertinent observations, made by separate speakers whose names are added in each instance.

Cardiac catheterization has given us great insight into the physiological adjustments taking place within the pulmonary circulation: pulmonary artery pressure remains stable in the face of wide variations in blood flow. Although the wedge or pulmonary capillary pressure is slow to follow the phasic changes in the left side of the heart it permits an estimate of pressure in the pulmonary veins. Catheterization of the coronary sinus is now facilitating a study of certain phases of the coronary blood flow and myocardial metabolism (Bing).

The electrocardiogram provides information which is often superior to that obtained radiologically in determining not only the presence, but also the degree of ventricular hypertrophy. One of the most pertinent electrocardiographic observations in healthy infants is the frequency of upright T waves in right chest leads during the first twenty-four hours after birth, and the progressive increased negativity of this deflection immediately afterwards. Combined enlargement of both right and left ventricles does not balance the electrocardiogram back to normal, for specific criteria should be in evidence for each separate entity (Ziegler).

In order to delineate more clearly the separate congenital malformations of the heart the contrast medium during angiocardiography should be injected as close as possible to the area under study. Thus, cardiac catheterization is first performed and a decision made on the site of injection (Jonsson).

Angiocardiography is a valuable form of investigation in patients with pulmonary stenosis in that actual atresia is present in 20% of cases of Fallot tetralogy when a direct operation on the valve is ineffective. Furthermore, shunt operations are not feasible unless there is an adequate pulmonary artery to accept the flow from a systemic artery (Keith).

A drawback to a direct operation on the valve in pulmonary stenosis is the resulting increased pulmonary flow which may accentuate the right ventricular preponderance in the electrocardiogram and cause further enlargement of the right ventricle (Brock).

Evidence is accruing that changes in the pulmonary vessels associated with congenital malformations of the heart are not necessarily a separate anomaly. A study of the small pulmonary arteries in congenital heart disease and their comparison with those of norma

children of similar ages confirms the view that changes in the pulmonary vascular bed result from two main influences, namely, a common systemic pulmonary ejectile force and a large pulmonary blood flow, each factor producing an increase in the pulmonary vascular resistance (Dammann). The prognosis in patients with free communication between the systemic and pulmonary circulation and a balanced blood flow, depends on whether the pulmonary hypertension has caused occlusive changes which have caused significant reduction in the size of the arterial bed, and such changes are usually met with in older patients (Edwards). The so-called reverse ductus with a high pulmonary resistance and with a pulmonary artery pressure which might exceed the aortic pressure should not be closed; even in one where the pressures are equal during a period of exercise, the ductus should be closed temporarily for twenty minutes in the first place when the tolerance of the right heart to the occlusion is watched (Muller).

Physiological studies of patients with mitral stenosis have confirmed that surgery can alleviate the pulmonary hypertension which it might have induced (Harvey). Seven adverse factors that influence the outcome of commissurotomy for mitral stenosis include age, fibrillation, associated incompetence of the valve or aortic valve disease, preoperative valve size of more than 1 sq. cm., postoperative valve size of less than 2·5 sq. cm., and calcification of the valve (Harken). Splitting of the commissure in mitral stenosis should be carried out to the annulus at the myocardium and the finger, passed through the new opening, should undertake a subvalvular dissection freeing the chordæ tendineæ from one another and from the wall of the ventricle (Glover).

Apart from the quotations given above, many if not most, of the difficulties and successes met in cardiovascular surgery are discussed by both physicians and surgeons of diverse creeds, and no one with an interest in the subject should be without this book.

Neural Control of the Pituitary Gland. By G. W. Harris, F.R.S., Sc.D., M.D. (Monographs of the Physiological Society No. 3.) (Pp. x + 298; 54 figs. 30s.) London: Edward Arnold (Publishers) Ltd. 1955.

This is a useful work. It provides a clear and concise account of the physiological relationships between the hypothalamus and the pituitary gland so far as they are known at the present time, and although it is primarily intended for advanced students who will eventually be engaged in research, it contains much that will interest clinicians in varied fields of work. It supplies in readable form a much-needed bridge between physiological experiments and everyday practice in medicine, surgery and obstetrics. Indeed it would be a pity if the title conveyed the impression that the book's appeal is exclusively to the endocrinologist and the academic neurologist, for this is far from being the case. A selective bibliography provides an entrance to the voluminous literature on the subject, but references to sources outside the Anglo-American orbit are so few that it might be questioned whether the net has been cast wide enough. With this one reservation, this monograph is warmly recommended to both clinicians and research workers, and the Physiological Society which sponsored it is to be congratulated on its choice of author.

Subphrenic Abscess. By H. R. S. Harley, M.S., F.R.C.S. (Pp. xii + 216; 35 figs. 35s.) Oxford: Blackwell Scientific Publications. 1955.

It is obvious from perusing the pages of this book that Mr. Harley has made a special study of the subject in all its aspects: historical, anatomical, ætiological; and in relation to the clinical features: radiological, complications, pre- and post-operative management and treatment. The monograph is based on a study of the records of 188 patients suffering from subphrenic abscess. The author, in the first instance, dealt with the subject in a Hunterian lecture. He has undoubtedly given a comprehensive picture of abscess-formation beneath the diaphragm and has clarified the anatomy of the subphrenic region in a manner which is of great practical advantage.

Both physician and surgeon could benefit by reading this work. The study of the radiological changes produced by subphrenic abscess is masterly in its comprehensiveness. The only criticism that one would offer is that the X-ray photographs, which are well reproduced and are all negative prints, would have been more conveniently placed in the chapter on radiological changes, but certainly in the text and not all at the end of the book.

Complications are carefully considered, and treatment is discussed in relation: (*a*) to the significance of chemotherapy and (*b*) in relation to the route of drainage. In this connexion, the author makes a strong plea for the universal adoption of extra-serous approaches to the subphrenic spaces.

The book can be thoroughly recommended; it is essentially readable, very practical, and a valuable contribution to this important subject.

Common Skin Diseases. By A. C. Roxburgh, M.D., F.R.C.P. 10th edition. (Pp. xxxii + 516; 215 text figures and 8 coloured plates. 30s.) London: H. K. Lewis & Co. Ltd. 1955.

It is a sad thought that Roxburgh will not be writing an eleventh edition of his book. Ten editions and eight reprintings in twenty-three years are ample testimony to its popularity. Yet the method of omitting outmoded sentences or paragraphs and replacing them with new thoughts and ideas to fit the spatial and financial ends of the publisher tends to destroy the wholeness of a book. The compactness of "Roxburgh" and its usefulness to the general practitioner have always been recognized; whoever is lucky enough to take on the task of a new edition will have to do some hard pruning to remove some of the untidy, excessive growth which is spoiling its shape. This applies particularly to the first fifty pages which are too discursive and out of date. The descriptions of diseases and their treatment are simply and easily given and the "small print" conditions are carefully avoided. The black and white photographs are excellent, the best things in the book. "Roxburgh" will continue to be popular with those for whom it is meant. It can only be hoped that future editions will be as gently written, as readable and a little shorter.

Cardiac Diagnosis. A Physiologic Approach. By Robert F. Rushmer, M.D. (Pp. viii + 447; illustrated. 80s. 6d.) Philadelphia and London: W. B. Saunders Company. 1955.

Although every physician acquires a knowledge of basic physiological principles, the author maintains that clinical diagnosis is still too largely dependent on correlating disease processes with characteristic symptoms and signs. The book, therefore, outlines an approach to cardiac diagnosis based on the function of the heart under normal and abnormal conditions, emphasizing the mechanism whereby disease produces its varied symptomatology. Since the heart is considered in its relation to the entire circulatory system, the first four Chapters (Part I) are devoted to the anatomical, physical and functional aspects of the whole cardiovascular system. Part II holds three chapters dealing with the regulation of the peripheral vascular system and of the heart, particularly emphasizing neural and hormonal control. In Part III congestive heart failure is examined. Old and new diagnostic methods are described and compared in Part IV, while their application to clinical problems is presented in Part V.

The book is profusely illustrated by useful diagrams. In the references priority has been given to recent publications and this decision has inevitably led to a neglect to mention earlier fundamental research in the several departments of cardiology. The bizarre presentation of cardiology instanced here may be disturbing to the clinician, but its explanation based on physiological principles makes its inevitable profitable contribution to clinical cardiology.

Munk's Roll. Vol. 4. Lives of the Fellows of the Royal College of Physicians of London 1826–1925. Compiled by G. H. Brown, M.A., B.Litt. (Pp. x + 637. £2 2s.) London: Royal College of Physicians. 1955.

Volume IV of William Munk's Roll of the Royal College of Physicians of London contains biographies of the 874 Fellows who were elected between 1826 and 1925 (excluding those who in 1826 were already licentiates). Mr. G. H. Brown, who has so admirably compiled this volume, has been at pains to preserve a certain standard of detail and uniformity of presentation throughout. The accounts, so succinctly and well written, succeed in that there is conveyed to the reader an impression, which at times is vivid, of each of these Fellows, their character, work, hobbies, environment and idiosyncrasies. The galaxy, which includes many "eminent Victorians", will introduce the reader to men who are commemorated at the College, such as Gavin Milroy, David Lloyd Roberts, George Oliver, Walter Moxon, Charles Murchison and William Baly. There is, too, an account of William Munk himself.

Fellows of the College were certainly pioneers in the field of chemistry and chemical pathology as is evident in the careers of B. G. Babington, Golding Bird, Henry Bence Jones, Alfred Garrod and his son Archibald, William Addison and J. L. W. Thudichum. Botany claimed others: Charles Morgan Lémann for instance, who bequeathed 30,000 specimens to Cambridge University and R. C. A. Prior (née Alexander) whose travels included a notable journey by ox wagon in search of South African plants. Several Fellows have had to retire early on account of illness only to survive into a healthy and profitable old age. J. L. Siordet was gravely ill with tuberculosis at the age of 30 but after a winter in Egypt he became a successful practitioner in Mentone where he died at the age of 83, while S. J. Goodfellow survived twenty-five years after a hemiplegia. Illness determined the careers of some of them, including W. J. Little, whose interest in orthopædics can be traced back

to his own attack of poliomyelitis, and Peyton Blakiston who, threatened with tuberculosis when an incumbent, was sent to Paris for treatment and there decided to make medicine his career.

Longevity in the profession seems to have been a feature of the more restful days of Victoria and Edward VII. Sir Henry Alfred Pitman, Sir Thomas Barlow and Sidney Philip Phillips all survived till their hundredth year, while Sir Hermann Weber who lived to be 93 was still an alpine climber at the age of 79. W. R. Basham however, was a valetudinarian who kept fit by bathing in the Serpentine, and who did not survive to the age he deserved.

Charles David Badham, after a career in medicine, became ordained and interested himself in natural history, while John Wale Hicks lived to become a bishop. Robert Bridges abandoned medicine to become Poet Laureate. C. J. B. Williams in retirement on the Riviera interested himself in sunspots and in a criticism of the revised version of the New Testament, while G. B. Longstaff took to entomology, municipal affairs and the special constabulary, which he joined at the age of 65.

Fellowship of the College is not, it seems, incompatible with a life of excitement. Sir Henry Jules Blanc studied at Montpellier, served in the Crimea and China wars and became surgeon to the mission in Abyssinia in 1864 when he was imprisoned and made to watch fellow prisoners being hurled over precipices. Later he was present at the battle of Magdala and then after a spell of removing bladder stones from wealthy Indian princes, settled down in delectable Cannes. Others have found excitement in exploring: J. Ormiston MacWilliam was on the ill-fated Niger expedition, but he lived to tell the tale. C. G. Seligman kept interrupting his professional career in order to explore the Torres Isles, Borneo and New Guinea, while Sir Alexander Armstrong kept his crew alive with lime-juice in the Northwest Passage and returned to take part in the Crimean war and finally at the age of 76 married for the first time.

Perhaps the most colourful personality of them all was Henri Guéneau de Mussy, descendant of a French court physician, who visited Ireland to study famine fever, which he himself contracted. In 1848 he accompanied Louis Philippe into exile and acquired a high professional reputation in London. He achieved the unique distinction of being entertained to a formal banquet at the College by the President and of having his coat of arms displayed in one of the windows. He returned to France in 1871 and in 1884 he attended the tercentenary celebrations of Edinburgh University and received an honorary degree.

Counseling in Medical Genetics. By Sheldon C. Reed. (Pp. viii + 268. 28s.) Philadelphia and London: W. B. Saunders Company. 1955.

There are now in the United States some twenty Heredity Clinics, many of them centred on University departments of genetics, where advice is given free on the many personal problems which can arise through the occurrence in the family of serious affections caused in whole or in part by genetic factors. Parents who have produced a child with hydrocephalus may want to know what the chance will be of another pregnancy resulting in a second deformed child; or an Adoption Society might enquire what was the chance of the child of an epileptic woman having fits, before deciding whether or not to recommend adoption. Among the first of these Heredity Clinics to be founded was the Dight Institute of the University of Minnesota, of which the author of this book is Director. He has written this small volume in plain and simple language, with the family physician in mind. Not only does he provide, from fourteen years' experience, the means of giving scientifically based and practical advice on a number of quite common problems, but he also summarizes and documents much of the literature on the inheritance of human diseases and malformations which has appeared in specialised journals in recent years.

The greater part of the book is taken up with the genetics and the risk figures for relatives of patients suffering from some twenty of the commonest conditions, about which advice has been sought at the Dight Clinic. It is interesting that the commonest of all problems referred to Dr. Reed is that of estimating the probable adult skin colour of an infant candidate for adoption: "Will he pass for White?" After this come epilepsy, consanguineous marriage, mental deficiency. At the end of the discussion in each chapter, there are illustrative examples, together with the advice given. There are also chapters on blood genetics, and on the genetic effects of radiation. In an appendix over 100 rarer conditions are listed, along with their mode of inheritance.

Dr. Reed considers that the overall effect of genetic counseling is to encourage people to have more children than they would have had otherwise, since they are usually more apprehensive than the facts warrant. Though our knowledge of human heredity is very sketchy, it is growing fast; the information accumulated and digested in this book shows that we already possess enough to aid the physician in a practical way.

Fractures of the Facial Skeleton. By N. L. Rowe, F.D.S. R.C.S., L.R.C.P., M.R.C.S., L.M.S.S.A., H.D.D. R.C.S.Ed., and H. C. Killey, F.D.S. R.C.S., L.R.C.P., M.R.C.S., L.M.S.S.A., H.D.D. R.C.S.Ed. (Pp. xxxvi + 923; 1231 illustrations, 14 in full colour. £6.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

The contributions of British Plastic and Dental Surgeons to maxillo-facial surgery have been so outstanding that a full record of their achievements was long overdue. As the years passed after cessation of hostilities and no further editions appeared of the books hurriedly produced during the war, it seemed that a great opportunity had been missed for want of authors prepared to face what had in fact become a major task.

Rowe and Killey not only face this task but succeed beyond expectation in producing a volume worthy of the subject. Very wisely they sought assistance of colleagues in covering some aspects of the subject and the contributions of Gillies, Clarkson, Ennis, Gilchrist, Holdsworth, McCash, Romanes and Walker add authority and distinction. O'Connell gave assistance in the preparation of the chapter on head injuries which succeeds in covering this important subject in a simple and effective manner. The authors show a commendably wide knowledge of the literature, both early and recent, and both classical and medical. There are references to almost every important paper on the subject, some being placed at the end of a chapter, some in the bibliography and some in both places. It is thus difficult to find some references and the authors might have followed the example of Watson-Jones, who writes a foreword, by replacing the bibliography with an index of authors. No subject is merely mentioned, detail is given to a degree not often encountered. The sections on electrolytic action, on the composition of casting metals and on radiography are examples.

The main point of criticism lies in the illustrations, which, as in so many British publications, are unworthy of the text. Having a wealth of photographs and radiographs at their disposal it was to be expected that the examples would be well chosen, but they are reproduced without the touching-up which is essential, and in consequence many are poor. Nowhere is this more noticeable than in the important section on splint construction and localization. Many of the radiographs would be more valuable if the fractures were outlined, and this applies particularly to the occipito-mental views.

For historical accuracy it is necessary to point out that the description of the reception of casualties from Normandy after D-day is not in accord with the organization set up by the Ministry of Health. At first six port hospitals were used but at an early date the work was centred at Cosham (where more than 140 cases were treated before transfer by train to distant centres). The evolution of specialized treatment for maxillo-facial injuries is described at length in the middle of the book, again in the historical background which forms the last chapter and also in the introduction. This interesting material should be grouped to form the first chapter and most of the statistics in the introduction relegated to an appendix. The simplest details of suture technique are given in chapter thirty-four although suturing is frequently mentioned before this. Post-operative care is given a chapter on page 684 and a main heading on page 635. With some rearrangement of the chapters it seems that the subjects might be developed in a more orderly manner and repetition avoided.

Most of the points mentioned are of minor importance and do not detract from the general excellence of the book. No criticism is applied to the details of diagnosis and treatment, which constitute a true record of past and present British practice in this specialty. The book should do much to further the art and enhance the prestige of British surgery.

An Atlas of Regional Dermatology. By G. H. Percival, M.D., Ph.D., F.R.C.P.E., D.P.H., and T. C. Dodds, F.I.M.L.T., F.I.B.P., F.R.P.S. (Pp. viii + 264; illustrated with 475 clinical subjects in full colour. £5.) Edinburgh & London: E. & S. Livingstone Ltd. 1955.

Herein are some 475 illustrations, regionally grouped, to show some of the diseases which may involve the skin. Some of the conditions are common, some are rarely seen. Some are pictured many times to show variations on themes; dermatitis herpetiformis appears seventeen times, pemphigus foliaceus eleven times, for instance. Most of the ordinary diseases are here, although lichen urticatus or bites are curiously absent. Under each picture is a title and a short descriptive note. Most of these are satisfactory enough but the terminology used for that vexing disease entity, eczema, is confusing to anyone south of the border. "Post-traumatic infective eczema" needs a little simplification or, is it, amplification to be understood without reference to a Scottish textbook? A more serious criticism, however, is the poor quality of some of the pictures. It is impossible to diagnose some of them; at least two dermatologists failed miserably in a test.

Accurate reproduction in colour of a large series of pictures is only possible at great expense, and, without accuracy so many pictures are worthless.

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SYMPOSIUM ON ACRYLIC RESIN FILLING MATERIALS

Mr. G. A. Morrant:

Composition and Activation

THE acrylic filling materials, in spite of differences between individual brands, have basically the same structure as the original heat-cured acrylic denture resins, and the familiar defects and limitations inherent in the nature of methyl methacrylate have not been eliminated in the newer form of the material.

In the first place there is a volumetric contraction in the monomer on conversion to polymer. This means that, unless compensated, there is a potential contraction in the filling of approximately 6%, which is only partially annulled by the subsequent expansion due to water absorption of 1·25% (Smith and Schoonover, 1953). The material is unfortunately soft in comparison with other filling materials and tooth structure, and is likely to wear under the forces of attrition and abrasion. Another property, which is of particular significance when the resin is applied to teeth in order to seal cavities, is its high differential thermal expansion over seven times greater than tooth structure (Nelsen *et al.*, 1952).

However, the particular feature of the acrylic filling materials which has distinguished them from their laboratory predecessors is the speed of polymerization. Great heat cannot be applied for a matter of hours in the mouth, nor can heavy spring pressure be used to assist in compensating for polymerization contraction. Instead, some form of chemical acceleration or activation is employed together with control of the shrinkage. This is effected by directing the polymerization towards tooth structure, either by chemical means again or by clinical technique.

Three distinct types of activator systems seem to have been evolved, based on an amine-peroxide reaction, sulphinic acid or a sulphur-peroxide system respectively.

In Type I about 0·5% of a tertiary amine is dissolved in the monomer liquid and about the same quantity of benzoyl peroxide is mixed with the polymer powder. On mixing, it is probable that the amine brings about a splitting of the unstable peroxide molecule. The free bonds of this split molecule (free radicle) attempt to saturate the double bond of the unsaturated carbon atoms in the acrylic molecule. These bonds are opened and polymerization is initiated (the so-called free radicle polymerization).

The earliest activators were aromatic amines (F.I.A.T., 1947) but it was found that these tended to discolour the resin, and aliphatic amines, such as N-trihexylamine, were next employed. However, these required treatment with an infra red lamp or an initial heat shock to stimulate the activation and were soon discarded. Manufacturers then reverted to aromatic amines, such as dimethyl-*p*-toluidine, but discoloration rapidly became a

major problem. This was probably due to subsequent oxidation of the amine. The manufacturer of one Type I resin claims to have overcome this by purifying the amine, which is easily contaminated by dimethyl-*m*-toluidine of similar boiling point. Stabilizing agents are also employed now in other resins using this activation system, while the addition of cross-linking co-polymers may also help the colour stability.

The second type of activation system was developed to avoid discoloration and speed the reaction, and was based on the use of para-toluene sulphinic acid which can initiate the polymerization of methylmethacrylate without the aid of additional substances (Hagger, 1951). However, sulphinic acid is unstable, easily being oxidized to para-toluene sulphonic acid, and so is supplied in an inert silicone base. Resins activated by this system are thus very susceptible to contamination by moisture during polymerization. In the Type II resin there is in addition an accelerator in the monomer liquid which is a trade secret, but it does not invalidate the above outline.

The high hopes of complete colour stability with this activator have been frequently disappointed. Discoloration may be due to the use of excess sulphinic acid catalyst, which is retained in suspension in the filling and is liable to decomposition. It may also be the result of too much hydroquinone inhibiter in the monomer, which can occur if monomer liquid is allowed to evaporate. An excess concentration of accelerator may then be present, in addition, and also have an adverse effect on the colour stability.

Ultraviolet light has a tendency to discolour acrylic and increase the breakdown of potential discolouring agents. A derivative of 2 : 4 di-hydroxy-benzo-phenone is now included in this resin and is supposed to counteract discoloration due to ultraviolet.

The third type of system is a modification of the first in which lauryl mercaptan, an aliphatic compound containing sulphur, is employed to react with benzoyl peroxide. The activator is contained in a separate tablet of compressed polymer, which is crushed and incorporated into the mix. Lauryl mercaptan is comparatively stable in storage and like the amines is not unduly affected by a small amount of moisture. It also appears to have good colour stability.

There remains the problem of shrinkage compensation. This may be achieved clinically, but in a number of products is assisted chemically. Thus, in one Type I resin, a liquid containing a high concentration of one of the activators is used on the cavity floor to commence polymerization at that surface first, so that any shrinkage is directed towards the walls of the cavity. The Type II resin has a special adhesive which is applied to the cavity and is then polymerized by the main mass of the filling material. Histological evidence shows that it does, in fact, have an effect on the dentine (Kramer and McLean, 1952). This adhesive is probably glycerophosphoric acid di-methacrylate.

The Type III resin contains methacrylic acid which has the effect of increasing the apparent adhesiveness of the resin, as well as speeding the set and producing a cross-linked polymer.

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Mr. Ivor R. H. Kramer:

Biological Considerations in the Assessment of Self-Polymerizing Acrylic Resins as Filling Materials

Of all the main classes of filling materials used in dentistry, only the self-polymerizing acrylic resins have received extensive laboratory investigation soon after their introduction and, in some cases, prior to their introduction, in an effort to determine their biological effects. I shall discuss the results of these investigations from the aspect of the irritancy of the materials. I shall not touch on the possible damage to the pulp which might result from the percolation of mouth fluids and mouth organisms between the filling material and the cavity walls.

It has already been pointed out that all these materials have certain basic constituents in common, at least one of which—the monomer—is an irritant. Therefore, it would hardly

be surprising if the various brands of self-polymerizing resins were found to have somewhat similar biological effects, and this has proved to be the case. Most of the brands on the market have been tested in experimental teeth which were subsequently examined histologically and, with a very few dissenting reports (Lefkowitz *et al.*, 1949; Seelig and Lefkowitz, 1950; van Huysen and Boyd, 1953), the majority of investigators have found each to be capable of causing pulp irritation. Some investigators have attempted to go further than simple tests for irritancy and inertness, and have tried to place the tests on a roughly quantitative basis so that the degree of irritation caused by the various brands could be compared (Kramer and McLean, 1952; McLean and Kramer, 1952; James *et al.*, 1954). These investigations indicate that, in general, the pulp reactions to all the resins activated by a benzoyl peroxide-tertiary amine system are similar, and that the reactions to the resin activated by para-toluene sulphinic acid is also of a similar degree and type. In connexion with this latter material (Sevriton) it is of interest to note that, when used experimentally in unlined cavities, the pulp response is the same whether or not the adhesive cavity seal is used (McLean and Kramer, 1952).

Interesting and unexpected results have been obtained with two materials containing methacrylic acid, for it appears that the presence of this compound may result in a type of pulp reaction quite different to that found with all the other materials. With most resins the pulp changes are of the types one would expect—dilatation of the vessels, infiltration of the tissue with inflammatory cells and sometimes secondary dentine formation. On the other hand, the response to the resins containing methacrylic acid is characterized by the development of large or small, single or multiple, blister-like fluid accumulations in the pulp, accompanied by remarkably little evidence of inflammatory cell infiltration (Kramer, 1954). The evidence has been briefly reported elsewhere (Kramer, 1955) and will shortly be published in detail. There appears to be little doubt that methacrylic acid is the resin component responsible for these curious lesions. The laboratory investigations do not indicate that they result in pulp death, and so far as I am aware the widespread clinical use of one of the methacrylic acid-containing materials by the dental profession has not produced any evidence that the proportion of restorations followed by pulp death is greater than with the other resin materials.

From the laboratory investigations we may conclude that all the self-polymerising resins so far marketed are potential irritants, and all are irritant to approximately the same degree (with the possible exception of those containing methacrylic acid, which cannot be compared directly with the others because the type of reaction is different). However, it is a point of some practical importance that the degree of pulp damage appears in most instances to be almost directly related to the proximity of the irritant material to the pulp. For any given resin, with a shallow cavity the pulp may escape unscathed whereas severe damage would result if the same material were placed unlined in a deep cavity. It is not unlikely that two factors are operating here, for one must not only consider the proximity of the material to the pulp, but also the greater volume of material likely to be contained in the deeper cavity.

Now we must consider how the results of these laboratory investigations should be interpreted in terms of clinical use. Because of the stringencies of the technique of the controlled experiment, most of the tests have been carried out in conditions which many practitioners may consider somewhat unrealistic, and this criticism is entirely justified although difficult to meet. Most investigators carried out their experiments using cavities cut in non-carious teeth, highly desirable if a controlled experiment is to be conducted, but not in accordance with normal clinical use. Therefore, it needs to be emphasized that it is unwise to assume that the pulp reactions in these research investigations will exactly reflect the pulp reactions to be expected with normal clinical use. Indeed, most research workers emphasize that they may not be the same. However, the investigations do give useful indications of potential irritancy, and the results obtained show that a lining material having as little irritant effect as possible should be used. Oxyphosphate cement is compatible with the resins, is the most commonly used lining material, and would appear to be reasonably satisfactory from the biological standpoint.

One further subject needs to be emphasized in this brief review. Recent laboratory investigations have shown again what has long been realized by most, but not all, clinicians—the absence of pain after filling cannot be taken as an indication that the pulp has escaped significant damage. The histological study of the pulp changes following filling has been compared with the patient's pain experience over the same period and it has been shown that severe pulp changes can be entirely symptomless (Kramer, 1954). It follows, therefore, that the irritant effects of new filling materials cannot adequately be judged without histological studies.

SUMMARY

Extensive investigations have shown (1) that all self-polymerizing acrylic resins so far marketed are probably sufficiently irritant to require a lining wherever possible, (2) that oxyphosphate cement, although not free from irritant properties of its own, has proved a reasonably suitable lining material from the biological point of view, (3) freedom from symptoms after filling is no adequate indication of absence of significant pulp damage.

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Mr. H. M. Pickard:

Clinical Evaluation

It is my task to summarize the value of autopolymerizing acrylic resin as a direct filling material, and I find that amongst practitioners there is a very wide divergence of opinion on this subject. The clinical characteristics derive directly from the physical, chemical and biological properties and are an immediate criterion of its value in restorative dentistry. It is therefore my purpose to relate these characteristics to its clinical behaviour.

Probably the most satisfactory aspect of this material is to be found in its æsthetic properties. When properly handled and uncontaminated it can produce restorations which blend remarkably well with the intact dental tissues. Subsequent discoloration of the mass due to chemical change, as has been referred to, has been largely eliminated, but failure in preparation of the cavo-surface angle and in manipulation are still causes of deterioration. Porosity from whatever cause, the retention of marginal flash, the occurrence of a marginal "ditch" and leakage are the common causes of various types of discoloration which may supervene with the passage of time.

The low values in hardness, strength and stiffness preclude the use of acrylic in stress-bearing restorations. To our great disappointment it has failed to solve the problem of restoration of the incisal angle, except as a temporary measure. Its use in this position in conjunction with gold introduces colour-matching difficulties which are not simple of solution, although its replacement at comparatively frequent intervals is fairly easy. There can be little doubt that it is seen to best advantage in Class III and Class V cavities, but in some of the latter its softness is a distinct disadvantage.

One of the least favourable characteristics of any restorative material is that of shrinkage upon setting. A volumetric reduction of 6 to 7% on polymerization arising from the physico-chemical change appears to be unavoidable with this material and various techniques are aimed at compensating for that property, by keeping the mass in close contact with the cavity walls and allowing shrinkage to take place in areas where it can be corrected by an excess.

The use of pressure and lamination techniques, including that first publicized by Nealon, have this as their object, whilst a cavity-sealing material, which, it is claimed, forms a molecular cohesion between tooth and filling mass, has been widely used with considerable success at the hands of many operators. I think it has yet to be convincingly demonstrated that any of the so-called pressure techniques do, in fact, result in a significant positive pressure within the polymerizing mass, and if they did so the setting up of internal stresses, with their subsequent effect on water absorption and warpage leave the desirability of such a procedure open to doubt. It may be that the most desirable aspect of these techniques is the immobility of the matrix during the crucial period of setting.

Another related hazard in the use of acrylic lies in the discrepancy of its coefficient of thermal expansion from that of natural tissues. It is true that few existing filling materials except silicate cement approach closely to the figures generally accepted for dentine and enamel, but a sevenfold difference seems a very large gap to bridge. We are therefore not surprised to learn of the phenomenon of seepage which has been demonstrated to occur over a range of temperature change which, you may consider, is probably rather greater than is commonly to be found in the incisor teeth. This little-known phenomenon of marginal percolation is now beginning to receive attention.

By the criteria of clinical observation many acrylic fillings appear to remain watertight for a considerable period of time. Indeed this receives some confirmation from *in vitro* experiments conducted by two members of this Section. The explanation of this apparent seal may lie in the efficiency of the bonding, either physical or chemical, of the filling to the cavity walls, and perhaps in the lower temperature range to which anterior restorations are actually subject. The third possibility is that seepage may, in fact, occur for varying periods of time without becoming clinically manifest as such.

The clinical recognition of seepage must obviously depend upon the tendency to staining and the caries-proneness of the individual; both of these are clearly variable factors. In the complete absence of both one could imagine that marginal percolation might continue undetected for very considerable periods. In mild instances of either a similar state might perhaps occur. One the other hand we know that marginal failure may occur within a disconcertingly short period and the practitioner, whilst blaming the inherent properties of the material may also admit the possibility of failure in manipulation. There seems to be a general consensus of opinion that caries recurrence is more common around acrylic than around silicate fillings. My experience does not convince me that this is so.

Several favourable properties of acrylic derive from: the inert character of the polymerized mass; it is insoluble in water and therefore not subject to surface dissolution; its low thermal conductivity; and its ability to remain comparatively unaffected by substances commonly ingested.

There is abundant histological evidence of the irritancy of this material during its insertion, and ample clinical experience of the occurrence of non-vital and moribund dental pulps. In this respect it may be claimed that the situation is no worse than with silicate cements and, but for the fact that zinc oxide and eugenol are debarred, this would seem to be so. The factors governing the avoidance of irritation would appear to be identical in the case of both materials, and I am again impressed by our need for a lining material which, while being non-irritant in itself, will provide an impermeable barrier, will have no deleterious effect on the filling, and will not significantly block out undercuts made for retention. There is one cement available which apparently approaches some of these criteria. Furthermore, the impregnation of dentine by zinc ferrocyanide precipitate may possibly have some claim in this field.

In terms of the technique of cavity preparation and the exclusion of moisture we again find virtually no difference in the handling of acrylic and the silicate which we hoped it might displace. The cavity for any plastic filling of low adhesiveness must be mechanically retentive and the requirements for acrylic are certainly no less demanding than those for the cement. Although moisture contamination is more noxious in the type of resin activated by sulphinic acid no one would claim that anything less than complete control of a dry cavity is a primary necessity.

Many operators have remarked upon the delay in polymerization in the case of fillings of minimal size. This is held to be due to the rapid conduction of heat away from such a filling and has resulted in the inadvertent dislodgment of a partially polymerized mass. Variations in behaviour due to high or low room temperature are a trap for the unwary and, where the prescribed technique has been followed with care, variation in setting characteristics lead the operator to the conclusion that some variability or deterioration in one or more of the components is the only reasonable explanation.

In this brief review of the clinical value of the material I must not fail to pay tribute to the workers who have been responsible for the development of a substance which at first appeared to be a marked advance in restorative technique. In a modified form it may yet prove to be so, but so far, it appears to be limited in its application, requiring a punctilious technique and, even so, susceptible to unforeseen failure.

A material designed for frequent use by the rank and file of practitioners should not throw demands upon the skill, time and application of the operator without some very marked advantage to be gained in its use. Such marked advantage cannot, I submit, be convincingly claimed in support of the autopolymerizing acrylic used as a direct filling material.

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[*Continued from p. 344*]

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